TEXAS REPORTS on BIOLOGY and MEDICINE

VOLUME 6, NUMBER 3 FALL, 1948

Contents

PAGE

EXPERIENCES IN ATTEMPTING TO ELUCIDATE CERTAIN OF THE MULTITUDINOUS FUNCTIONS OF THE PITUITARY GLAND, USING THE EXPERIMENTAL SURGICAL APPROACH, *Allen D. Keller* 275

THE PHARMACOLOGY OF ANTIBIOTICS, *Hans Molitor* 291

THE NEED FOR PHYSICAL MEDICINE REBABILITATION IN GENERAL PRACTICE AS INDICATED BY THE EXPERIENCE OF THE VETERANS ADMINISTRATION, *A. B. C. Knudson* 302

AGE AND THE ENDOCRINE GLANDS, *C. E. Hall* 321

MEDICAL ASPECTS OF THE TEXAS CITY DISASTER WITH SPECIAL REFERENCE TO THE EFFECTS OF AIR BLAST, *David Minard, John H. Killough and Bernard Zimmerman* 337

DETERMINATION OF CODEHYDROGENASE I (COZYMASE) IN TUMOR TISSUES, *A. Fisher and F. Schlenk* 346

CORTICAL ATROPHY AS THE ETIOLOGICAL FACTOR IN CERTAIN TYPES OF MENTAL DISORDERS, *Jack R. Ewalt and L. C. Hanes* 354

DOES LIGATION OF PERIADRENAL TISSUES PRODUCE ELEVATION OF BLOOD PRESSURE? *Eric Ogden, Eleanore Tripp, W. Doyne Collings and Joseph Victor* 364

REPORT OF CASE OF PRIMARY PAPILLARY ADENOCARCINOMA OF DUODENUM, WITH SPECIAL REFERENCE TO X-RAY STUDY, *Jesse B. Johnson* 373

THE INHIBITORY EFFECT OF ANTIORGAN SERA ON EXPERIMENTAL RICKETTSIAL INFECTIONS IN THE PRESENCE OF TESTICULAR EXTRACT, *Ludwik Anigstein and Dorothy Whitney, with Technical Assistance of Norma W. Hansen* 379

AN EFFECTIVE ANTIVIRAL SYNTHETIC, *Murray Sanders, Y. SubbaRow and R. C. Alexander* 385

CALLING ATTENTION TO 396

COPYRIGHT 1947
BY
THE BOARD OF REGENTS
OF
THE UNIVERSITY OF TEXAS

EXPERIENCES IN ATTEMPTING TO ELUCIDATE CERTAIN OF THE MULTITUDINOUS FUNCTIONS OF THE PITUITARY GLAND, USING THE EXPERIMENTAL SURGICAL APPROACH

ALLEN D. KELLER*

In considering a subject for discussion, it occurred to me that you might be interested in hearing some of our experiences in attempting to elucidate further pituitary functions by the surgical approach. The extirpation approach to the function of any anatomical structure is directly that of attempting to precipitate functional deficits encountered clinically; therefore the problem holds equal interest to both the clinical diagnostician and the physiologist.

PITUITARY VERSUS HYPOTHALAMIC FUNCTIONS. The interpretation of results obtained in using the surgical approach upon the hypophysis has been troublesome because of the eternal suspicion that a surgical procedure upon the pituitary is impossible without concomitant functional infringement upon the neighboring hypothalamus. This suspicion has been particularly prominent in the critical analysis of work done on the dog. The problem has therefore been primarily one of distinguishing between pituitary and hypothalamic functions. The manner in which opinion regarding pituitary versus hypothalamic deficits has fluctuated since 1900, on the basis of conclusions drawn by representative responsible investigators, is briefly as follows.

The impetus to investigate experimentally the functions of the pituitary-hypothalamic region came from clinical observation. During the late part of the last century clinicians began realizing that bizarre multiglandular clinical entities were associated with pathology at the brain base. Speculation naturally arose as to whether these conditions were due to brain

*Lecturer in Physiology, The University of Texas School of Medicine, Galveston, Texas. Delivered at the Annual Dinner Meeting, Dallas County Medical Society, Dallas, Texas, January 8, 1948.

or pituitary derangements. The predominant thinking was that these disturbances had an endocrine or pituitary basis. The origin of the adenohypophysis from embryonic gut and its adult cellular histology suggested that it was an endocrine gland.

The first experimental work of consequence on the effects of surgical removal of the hypophysis was reported by Cushing and associates[1] in 1910. They encountered the adiposogenital syndrome in the dog and without question associated it with removal of the hypophysis and not with neighboring disturbances in hypothalamic function. Aschner[2] in 1912 also encountered this syndrome in dogs following hypophysectomy, but felt for some unknown reason that it was due to inadvertent functional encroachment upon the hypothalamus. Aschner was the first to demonstrate dwarfing in puppies which he was equally convinced was an uncomplicated pituitary deficiency.

Camus and Roussy[3] in 1920 and Bailey and Bremer[4] in 1921 completely swung the pendulum to the hypothalamic concept when they reported precipitating sexual regression and obesity —and, they believed, also dwarfing—by lesions confined to the hypothalamus. The influence of such thinking was, however, short-lived. The first opposing voice came from Evans[5] in 1924 in the following words: "As a result of experimental surgery of the brain it has recently been announced that most, if not all, of the features of the so-called hypophysial syndromes are due to brain lesions. I do not believe that this is true."

The swing back to thinking in terms of hypophysial deficits was, however, largely due to Smith's[6] introduction of his now classical surgical approach to the pituitary in the rat. This approach was immediately held to be foolproof against hypothalamic encroachment and in addition was said to render a reliably reproducible "constant hypophysectomy syndrome." Smith agreed with Cushing and Aschner that hypophysectomy produced sexual regression and dwarfing. In addition he added atrophy of the adrenals and thyroids. But he relegated obesity to hypothalamic involvement as had Aschner, Camus, and Bailey, even though he produced obesity by injecting chromic acid directly into the pituitary gland, *i.e.*, below the connective

tissue septum, and in so doing produced a *graded type* of hypophysectomy!

Houssay[7] added disturbances in carbohydrate metabolism of two separate and distinct categories: First, there is an immediate marked decrease in carbohydrate stores of the body as shown by (1) spontaneous hypoglycemic crises, (2) hypoglycemic crises precipitated by withholding food, (3) lowered liver and muscle glycogen, and (4) marked decrease in the ability to tolerate a given dose of insulin. Second, there is an immediate amelioration of pancreatic diabetes as shown by (1) absence of or decrease in hyperglycemia and glycosuria, (2) absence of or decrease in ketonemia and ketonuria, (3) less rapid loss of body weight and subcutaneous and intra-abdominal fat stores, (4) increased length of life of the animal, and (5) absence of or decrease in the amount of fat in the liver.

These deficiencies have all been conclusively identified with the anterior lobe of the pituitary because they have been alleviated by appropriate anterior lobe substitution therapy. This over-all deficiency complex is then solidly aligned with uncomplicated hypopituitarism, a deficit complex which clearly has an endocrine basis.

But, what is the corresponding situation with respect to deficiency symptoms which follow lesions confined to the hypothalamus and which clearly have a neurogenic basis? Although there are several functional deficits currently accredited to have a hypothalamic-neurogenic basis, there is only one deficiency symptom which has been *conclusively* shown to be due to hypothalamic destruction and to be a neurogenic deficit. This is a deficiency in the ability to regulate body temperature.*

In between these established pituitary-endocrine deficits and this established hypothalamic-neurogenic deficit, there still remains much confusion of thought. For example, the following questions and others are still before us. Is hypothalamic obesity a neurogenic or an endocrine deficit, or both? Sex

*This statement should not be interpreted as implying that the hypothalamus has only one neurogenic function. It also should be borne in mind that so-called irritative stimulator effects are not under discussion.

atrophy is solidly aligned as a pituitary deficit, yet it is currently accepted that lesions restricted to the hypothalamus will also cause sexual atrophy. Is there then in addition to a pituitary-endocrine sex deficit also a hypothalamic-neurogenic sex deficit, or is the sex atrophy following a hypothalamic lesion also an endocrine deficit?

My first interest in the pituitary led directly from early attempts to evaluate the effects of traumatic lesions placed in the hypothalamus. I continually found myself faced with the suspicion that perhaps it is just as, if not more, impossible to place hypothalamic lesions without concomitant functional infringement upon the neighboring pituitary gland as the vice-versa suspicion alluded to previously.

For instance, an early problem was that of evaluating gastrointestinal ulceration, first encountered following hypothalamic lesions[8] and later following hypophysectomy[9] in the dog. It seems safe to conclude that this ulceration was due to the same underlying disturbance, since the same end result obtained in each instance. The question was whether the ulceration was due to a neighboring infringement upon the hypothalamus following the hypophysectomy or to a neighboring infringement upon the pituitary following the hypothalamic lesion. Was the ulceration due to an underlying *neurogenic* derangement or to an underlying *endocrine* derangement? It is true that the ulceration seemed best explained on a neurogenic basis because of the well-known fact that nerve cells in the hypothalamus have a rich synaptic connection with the entire autonomic outflow, and in addition strong evidence was presented indicating that the ulceration was the result of a neurogenic derangement.[10] This instance illustrates well the point that the problem of distinguishing between purely hypothalamic and purely pituitary disturbances is difficult and real.

Unitary Versus Multiple Factors. It rapidly became obvious that it would be necessary for us to have a knowledge of the effects of graded infringements upon the pituitary before we could move forward confidently with the evaluation of the effects of hypothalamic lesions. The literature gave us no help, because such was essentially non-existent. We accordingly

decided to venture upon a long-term program of experiments upon the pituitary which we hoped would be clarifying.

We desired to ascertain if it were possible, by graded surgical infringement upon the pituitary, to precipitate individual, or individual groups of, pituitary deficits without a corresponding degree of deficit in other pituitary functions; or, if one encounters uniformly the same magnitude of deficiencies in all target organs and mechanisms in uncomplicated hypophysial disease and following an uncomplicated graded hypophysectomy procedure. This problem is none other than the longstanding question of whether the adenohypophysis elaborates one or two mother substances or multiple independent substances; or, in terms of the experience of the endocrine chemist, whether, in isolating individual target organ fractions from total pituitary extracts, a mother substance has been "chemically dissected" or the already individual substances simply isolated one from the other. Stating the problem in still another way, we desired to ascertain whether the established pituitary deficits could be to any extent surgically or physiologically dissociated or dissected in terms of isolated, permanent, and assayable deficits.

The dog was used by preference because direct visibility of the entire gland and its connections with the hypothalamus can be accomplished better than in any other laboratory animal. Direct visibility is a necessary requisite for executing graded hypophysectomies of the type which we attempted and accomplished. These are schematized in the drawing shown in Figure 1. We sought descriptive terms which by themselves would describe the amount of the gland removed as delimited by the lines numbered from 1 through 6 in Figure 1. We finally decided upon a *purely arbitrary* terminology based upon the current usage of the term hypophysectomy; namely, that total removal of the pars anterior is *ordinarily* considered a total hypophysectomy. Thus the terminology near-ordinary, ordinary, ordinary-plus, near-total, total, and total-plus hypophysectomies.

It was found that by executing these varying grades of hypophysectomy, one could literally surgically or physiologically "dissect" to a considerable degree the various established

hypophysectomy deficits.[11] The results can best be summarized around the operation type.

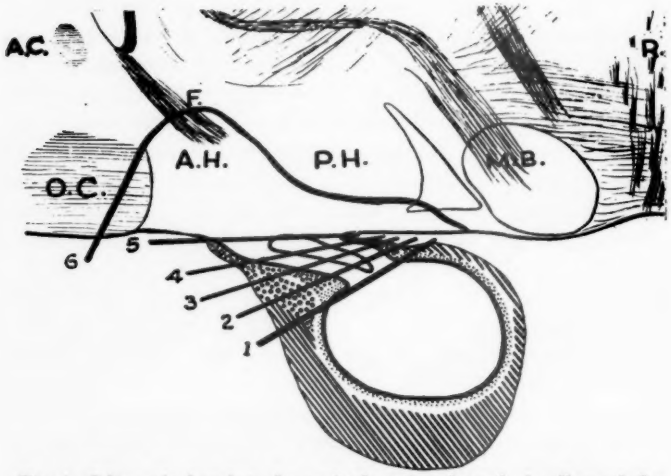


FIG. 1. Schematic drawing of a sagittal section through the diencephalon and hypophysis of the dog, on which the different types of hypophysectomy are indicated by lines 1 to 5.

Near-ordinary hypophysectomy. Following near-ordinary hypophysectomy, immediate and complete dwarfing and usually sexual regression occurred. However, the physiological dissection of the growth factor from the gonadotropic factor was clearly accomplished in our experiment 51-H.[12] A verified near-ordinary hypophysectomy was executed in this puppy when 3 months of age. It at once ceased growing in body stature as shown in the photograph taken alongside its unoperated male litter mate at the age of 10 months (Fig. 2). Yet it developed normally sexually as shown by the photograph of its genital tract and ovaries alongside those of a litter mate which died when 3½ months old (operation age) (Fig. 3). The external genitalia and vagina of this dwarf were not dwarfed in any way and were so large that they protruded and hung pendant like testicles. Typical signs of estrus were exhibited at regular 6-month intervals. Histologically, the

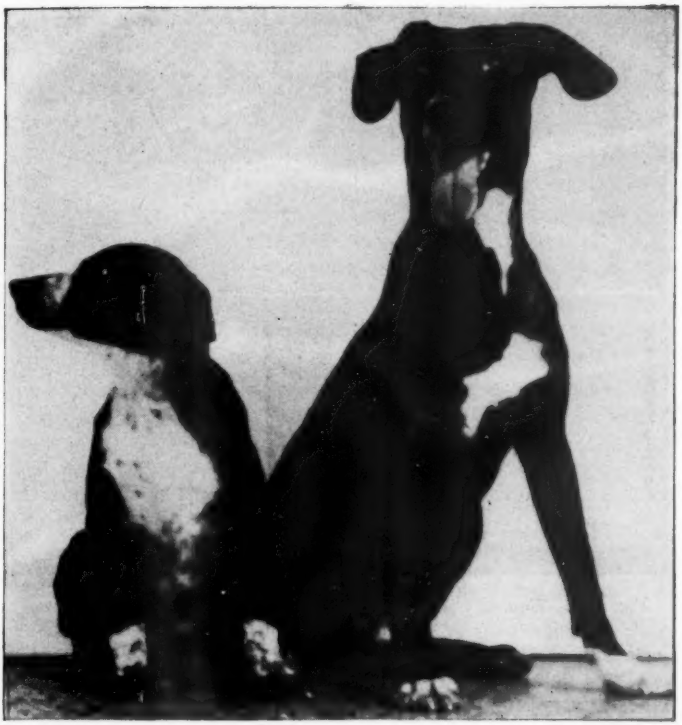


FIG. 2. Litter mates, 51-H (left) and 58-H (right) at 9½ months of age and 6½ months after near-ordinary hypophysectomy in 51-H.

remnant of pars anterior which remained possessed many normal-appearing basophiles, but essentially no acidophiles. *In this instance the growth factor was dissected free from the rest of the total hypophysectomy complex.*

Carbohydrate metabolism in this type of preparation was disturbed only slightly. The tolerance for insulin was reduced from 2 to 10 times, but the amount of reduction was slight as compared with a maximal deficit. There were no other assayable signs of pituitary deficiencies.

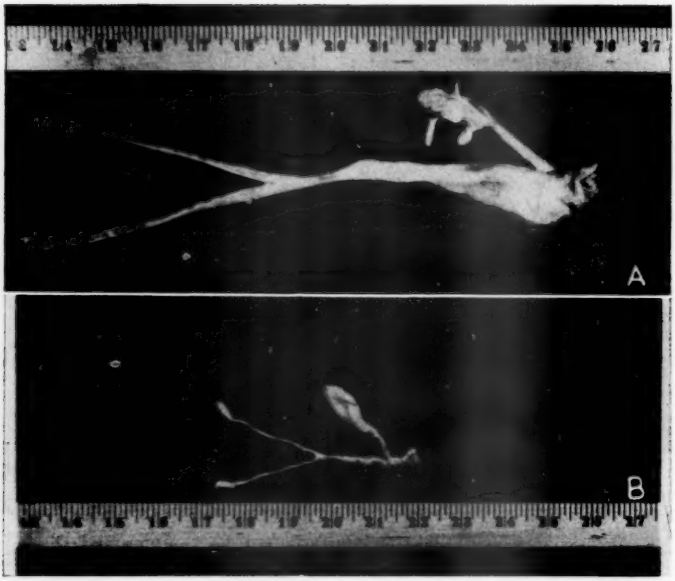


FIG. 3. A. Genital tract and bladder of dwarfed dog 51-H at 20 months after hypophysectomy at 3 months. B. Genital tract and bladder of litter mate 56-H at 3½ months.

Ordinary hypophysectomy. In this type of preparation, growth, and sex deficits were fullblown; yet the other deficits of the hypophysectomy complex, save for a reduction in insulin tolerance of only 10 times, were not in evidence. Thus, by removing all the pars anterior and leaving the larger portion of the pars tuberalis intact, *the growth and gonadotropic factors were dissected free from the other deficits in the complex.* This, from the physiological and anatomical points of view, was a surprising observation because current thinking allocates the entire hypophysectomy deficit-complex solely to the removal of the pars anterior.

Ordinary-plus hypophysectomy. In an ordinary-plus type of hypophysectomy, it was possible in instances *to dissect out a well-marked Houssay effect* without any greater reduction in insulin tolerance than was present in an ordinary hypophy-

sectomy and without detection of signs of hypoadrenalism. Frequently, however, there was a greater reduction in insulin tolerance than was usually encountered in ordinary or near-ordinary preparations. Although at autopsy the adrenal cortices were thinner than normal, this thinning was far from maximal, and the tissue was still functionally adequate to meet the severe surgical stress of pancreatectomy.

I am inclined to believe that an ordinary-plus hypophysectomy in the dog paralleled more nearly than any other types described herein the kind that is usually attained in the rat when the suction method of Smith is used. To wit this quotation from Collip:[13] "Monkeys, rabbits, dogs, guinea-pigs, birds, and toads frequently develop fatal hypoglycemia unless glucose is administered during the recovery period. Hypophysectomized rats, however, are rather exceptional, *since they withstand fasting better than other species and rarely manifest clinical signs of hypoglycemia.* Their muscle and liver glycogen is nevertheless greatly reduced." (Author's italics.)

Near-total hypophysectomy. In this type of hypophysectomy, the animals under stress succumbed to adrenal insufficiency crises, and the reduction in carbohydrate stores, the Houssay effect, and adrenal cortex thinning were all marked, but still were not maximal.

The tendency to spontaneous hypoglycemic crises was so great that it was necessary to feed the animals every 8 hours to keep them alive. When insulin tolerance was assayed—8 hours after feeding rather than the usual 24 hours—the animal was unable to tolerate 1/40 to 1/60 unit of insulin per kg. of body weight. This is a reduction in insulin tolerance of at least 100 times. In order to demonstrate the Houssay effect, one must execute the pancreatectomy previous to hypophysectomy. When this is done, the Houssay effect is still not maximal, as shown by a slow but progressive fall in body weight, and at autopsy the liver has a yellowish tinge.

Adrenal function was still adequate for indefinite maintenance under ordinary conditions, but was not sufficient to meet the surgical stress of pancreatectomy. Even when tolerance for insulin was returned to near-normal by anterior pituitary extract therapy, the adrenal function still remained inadequate

for this stress. At autopsy the adrenal cortices were found to be markedly, though not maximally, thinned.

Uncomplicated total hypophysectomy. In this preparation the entire classical hypophysectomy deficit-complex was present in its maximal degree, and the adrenal and carbohydrate deficits were more profund, we believe, than has hitherto been appreciated.

In order to keep these animals alive, particularly in the presence of pancreatectomy, blood sugar had to be maintained by keeping food in the digestive tract continually. Pancreatectomy produced no detectable alteration in carbohydrate and fat metabolism. Body weight was maintained, and at autopsy the liver showed no yellowish tinge. The effect on carbohydrate metabolism appeared to be completely equivalent to total removal of the liver. We conclude that uncomplicated total hypophysectomy is incompatible to the life of the animal unless its blood sugar is maintained in a semi-artificial manner.

The adrenal atrophy deficit was also maximal, but this was not an immediate effect as was the carbohydrate deficit. The animals got along adequately for 3 to 4 weeks before spontaneous adrenal insufficiency crises appeared, and at autopsy the cortices were found to be thinned maximally (Fig. 4). It is

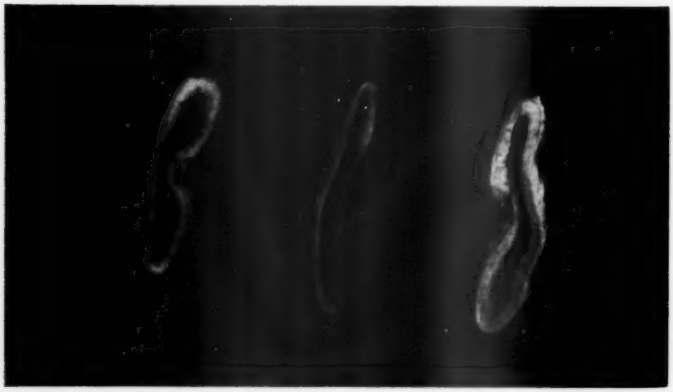


FIG. 4. Left adrenals of 3 adult dogs maintained for 6 months after total (middle) and total-plus hypophysectomies (left and right).

concluded that uncomplicated total hypophysectomy is incompatible to life for longer than 4 to 6 weeks without appropiate adrenal cortex substitution therapy.

Total-plus hypophysectomy. We succeeded in maintaining several animals for a long period following attempted total hypophysectomy plus purposeful infringement upon the hypothalamus. These animals failed to display certain of the pituitary deficits, yet did exhibit other deficits in fullblown form. They exhibited (1) sexual regression, (2) a maximal change in coat which seemed to be associated with the growth factor, (3) obesity, (4) lowering of basal metabolism by 30%, and (5) permanent diabetes insipidus. They did not show evidence of adrenal hypofunction since they lived indefinitely without adrenal cortex therapy and, in addition, withstood the severe surgical stress of pancreatectomy without signs of adrenal insufficiency. At autopsy the adrenal cortices showed only moderate or no atrophy (Fig. 4). Nor did they exhibit any striking disturbance in carbohydrate metabolism. There was no tendency to hypoglycemia; they lived indefinitely on a regular once-in-24-hours feeding schedule; and their sensitivity to insulin was near-normal or definitely not increased to the maximal extent.

Regardless of the ultimate explanation as to the why of these preparations, we do have here on an experimental basis the seemingly paradoxical situation of "*Pituitary destruction without pituitary symptons*" that Bailey and Bremer imply occurs on occasion clinically.[4] There is no doubt in my mind that this is the type of hypophysectomized dog preparation which many investigators have worked upon, and is one of the reasons why there has been so much controversy about work done upon the dog. Note particularly Aschner's finding of adrenal cortex hypertrophy rather than atrophy following hypophysectomy; Reichert and Dandy's dogs which were sent to the country and boarded out with friends as pets (*i.e.*, without special feeding and environmental care) following total-plus hypophysectomies;[14,15] and Heinbecker and Rolf's totally hypophysectomized animals having a reduction in insulin tolerance of *only 4 times!*[16]

In my preparations of this type, on serial sectioning of the fossal contents, a small remnant of mixed pituitary tissue was found in the distal scar tissue. The question arose, therefore, as to whether the failure of full-blown adrenal cortex and carbohydrate deficits to appear was a result of the hypothalamic encroachment or was due to an unusually potent selective activity of the speck of remaining pituitary tissue. These were the only two variables that deviated from the uncomplicated total hypophysectomy.

The fact that we have not as yet succeeded in maintaining such preparations without a remnant being present and the long-established knowledge that remnants of endocrine tissue must not be ignored under any circumstances has caused us to proceed with extreme caution in evaluating these preparations. This is particularly so because our own experience has shown that *normal or near-normal carbohydrate and adrenal cortical functions can be retained in the presence of full-blown growth and sex deficits* both in ordinary hypophysectomized preparations and after the isolation of the distal portion of the pars anterior by a stalk removal procedure.[17] In spite of these observations, I still doubt that the remnant of glandular tissue —because of its minute size—could be sufficient to maintain a normal or near-normal carbohydrate metabolism and adrenal cortex. In this connection, attention should be called to the fact that if the contra-principle concept holds (depicted below), then a small functional remnant of the pars anterior would have an effect greatly out of proportion to that which it would have if the appropriate contra-principle or principles were still being elaborated. Accordingly, the explanation might well *encompass a mutually reinforcing combination of both variables.*

Assuming that the minute remnant is not the whole explanation, we have speculated as to how the hypothalamic encroachment could *reverse* or aid in reversing such vitally important and severe deficits. It isn't logical to think in terms of an explanation on a neurogenic basis. It seems therefore best to begin thinking in terms of the *hypothalamus being an endocrine organ* in addition to a neurogenic center. These reversal effects could then be explained by postulating that there are elements in the hypothalamus which elaborate endocrine principles

having actions opposite to certain of the known hypophysial principles. This is using Collip's theory of antihormones.

On the basis of this hypothesis, the atrophy of the adrenal cortex following uncomplicated total hypophysectomy would be due to the continued unopposed activity of the contra-adrenotropic principle being elaborated from a site in the undisturbed hypothalamus. In the event that both the adrenotropic principle and the contra-adrenotropic principle were simultaneously eliminated (total hypophysectomy plus infringement upon the hypothalamus), adrenal atrophy would not occur; *i.e.*, the cortex would maintain a status quo, or at least the atrophy would not be maximal. On the other hand, if the contra-adrenotropic principle were eliminated or impaired by a lesion restricted to the hypothalamus, without there being a corresponding impairment of the elaboration of the adrenotropic principle, hypertrophy of the adrenal cortex would result, and with it hyperadrenalism or Cushing's syndrome. Here would be an end result simulating a hyperactive adenoma without actual hyperactivity of the elaborating cells in the true sense.

The idea of the hypothalamus possessing endocrine functions may seem rather far-fetched, but histological support for this probability is not lacking, and the evidence that hypothalamic tissue can and does elaborate the antidiuretic principle is irrefutable.[18,19] Scharrer[20] has described in the hypothalamus cells containing intracellular granules of the type ordinarily correlated with a secretory function which he calls "secretory neurons." My colleague, C. G. Breckenridge,[21] is in the process of exploring systematically the hypothalamus of the dog with a view of determining the location of and the types of granule-bearing cells. He has found five distinct cell types, two of which are particularly prominent in certain nuclei of the hypothalamus and in the infundibulum of the dog. The most numerous cell type is dark-staining with small spherical basophilic granules. The second most numerous cell-type has in its cytoplasm large, discrete, spherical acidophilic granules which extend out into the long cell processes. This cell is Scharrer's "secretory neuron."

Conclusions

There are many implications and ramifications of the material I have presented which I shall not discuss, but in conclusion I should like to emphasize the following points:

1. One should be just as suspicious of neighboring functional infringement upon the pituitary in the presence of primary hypothalamic pathology as of neighboring hypothalamic infringement following primary pituitary pathology. Certainly encountering an isolated deficit or group of deficits without the entire hypophysectomy complex being involved equally cannot necessarily be interpreted as being pathognomonic of a primary hypothalamic involvement, as has been the tendency in the past.

2. It is clear that all hypophysectomy deficits are not due solely to the absence of the pars anterior; the pars tuberalis is equally important. We suggest including the pars tuberalis with the pars anterior under the designation of anterior lobe, rather than anterior lobe being synonomous with pars anterior.

3. Maximal adrenal and carbohydrate metabolism hypophysectomy deficits are incompatible to the life of the animal.

4. I am strongly suspicious that Collip's theory of antihormones is a reality, and further that the hypothalamus is the site of elaboration of endocrine principles which are closely related to the principles known to be elaborated by the adrenohypophysis. I again, and for a different reason, suggest that the hypothalamus be included in pituitary terminology as a component part of the neurohypophysis.[18]

5. I am sure that clarifying aids in our investigation of brain base functions would be for us (1) to begin talking and reasoning in terms of endocrine versus neurogenic deficits rather than pituitary versus hypothalamic deficits, and (2) to concentrate on the *why of the variability* of the multiglandular deficiency syndromes which are encountered in the presence of brain base pathology, rather than upon the "constancy of the hypophysectomy syndrome" in the rat.

BIBLIOGRAPHY

1. Crowe, S. J., H. Cushing, and J. Homans: Experimental hypophysectomy. Bull. J. Hopkins Hosp. *21*:127, 1910.

2. Aschner, B.: Über die Funktion der Hypophyse. Pflüger's Arch. Phys. *146*:1, 1912.
3. Camus, J., and G. Roussy: Experimental researches on the pituitary body. Diabetes insipidus, glycosuria, and those dystrophies considered as hypophyseal in origin. Endocrin. *4*:507, 1920.
4. Bailey, P., and F. Bremer: Experimental diabetes insipidus. Arch. Int. Med. *28*:773, 1921.
5. Evans, H. M.: The function of the anterior hypophysis. Harvey Lectures *19*:212, 1923-24.
6. Smith, P. E.: Hypophysectomy and a replacement therapy in the rat. Amer. J. Anat. *45*:205, 1930.
7. Houssay, B. A., and A. Biasotti: The hypophysis, carbohydrate metabolism, and diabetes. Endocrin. *15*:511, 1931.
8. Keller, A. D.: Ulceration in digestive tract of the dog following intracranial procedures. Arch. Path. *21*:127–164, 1936.
9. Keller, A. D., and M. C. D'Amour: Ulceration in the digestive tract of the dog following hypophysectomy. Arch. Path. *21*:185, 1936.
10. Keller, A. D.: Protection by peripheral nerve section of the gastrointestinal tract from ulceration following hypothalamic lesions. Arch. Path. *21*:165, 1936.
11. Keller, A. D., W. E. Lawrence, and C. B. Blair: Effects of varying degrees of hypophysectomy in the dog. Arch. Path. *40*:289, 1945.
12. Breckenridge, C. G., and A. D. Keller: Immediate and permanent dwarfing with subsequent sexual development following near-ordinary hypophysectomy in three-months-old female puppy. Fed. Proc. *6*:81, 1947.
13. Collip, J. B.: Results of recent studies on anterior pituitary hormones. Edin. Med. J. *45*:782, 1938.
14. Dandy, W. E., and F. L. Reichert: Studies on experimental hypophysectomy. I. Effect on the maintenance of life. Bull. Johns Hopkins Hosp. *37*:1, 1925.
15. Dandy, W. E., and F. L. Reichert: Studies on experimental hypophysectomy. III. Somatic, mental, and glandular effects. Bull. J. Hopkins Hosp. *62*:122, 1938.
16. Heinbecker, P., and D. Rolf: Hypophyseal eosinophile cell and insulin sensitivity. Amer. J. Physiol. *141*:566, 1944.
17. Keller, A. D., and C. G. Breckenridge: Retention of normal insulin tolerance and adrenal cortex after extirpation of hypophysial stalk in the dog. Amer. J. Physiol. *150*:222, 1947.
18. Keller, A. D.: Elimination of the pars nervosa without eliciting diabetes insipidus. Endocrin. *30*:408, 1942.
19. Handley, C. A., and A. D. Keller: Morphine induced secretion of pitressin in dogs with hypophyseal stalk in section. Fed. Proc. *6*:121, 1947.
20. Scharrer, E., and B. Scharrer: Secretory cells within the hypothalamus. Assoc. Res. in Nerv. and Ment. Dis. Vol. XX, p. 170, 1940.

21. Breckenridge, C. G.: Intracellular granules in the hypothalamus and infundibulum of the dog. Fed. Proc. *6*:81, 1947.

LEGENDS FOR ILLUSTRATIONS

FIGURE 1

Semi-schematic drawing of a sagittal section through the diencephalon and the hypophysis of the dog, on which the different types of hypophysectomy are indicated by lines 1 to 5. Removal of the tissue distal to line 1 constitutes a near-ordinary hypophysectomy; that to line 2, an ordinary hypophysectomy; that to line 3, an ordinary-plus hypophysectomy; that to line 4, a near-total hypophysectomy; and removal to line 5, a total hypophysectomy. Infringement upon the hypothalamus to any extent beyond line 5 and extending to line 6 constitutes a total-plus hypophysectomy. Line 6 represents the maximum involvement of the hypothalamus that we have found thus far compatible with maintaining the animal to a chronic state.

Solid lines—pars anterior; large dots—pars tuberalis; small dots—pars intermedia; white area distal to line 1—infundibular process; white area between lines 5 and 1—infundibulum. O.C. is the optic chiasm; A.H., the anterior hypothalamus; P.H., the posterior hypothalamus; F., the fornix; A.C., the anterior commissure; M.B., the mammillary body, and R., the red nucleus.

FIGURE 2

Photograph of litter mates, dog 51-H (female) on the left, and dog 58-H (male) on the right, taken when 9½ months of age and 6½ months after dog 51-H was surgically deprived of the portion of its hypophysis distal to line 1 in Figure 1 (near-ordinary hypophysectomy). Note the definite and striking dwarfing of the body growth which obtained in the operated pup.

FIGURE 3

A. Photograph of the genital tract and bladder of the dwarfed pup 51-H at the age of 23 months (the dog was operated when 3 months old). *B*. Photograph of the genital tract and bladder of dog 56-H, a litter mate, at the age of 3½ months. It is to be noted that there was no dwarfing of the genital tract in the pup otherwise suffering from a complete and permanent dwarfing, which is reflected in these photographs by bladder size.

FIGURE 4

Photographs of the left adrenals of three adult dogs which were maintained 6 or more months following hypophysectomy procedure. The adrenal in the middle shows the maximal degree of cortical atrophy that we have encountered, and this was in a dog having a near-total hypophysectomy that approached a total hypophysectomy; whereas the other two adrenals are those from dogs which had total-plus hypophysectomies, except for a very small fragment of mixed pituitary tissue found in the distal scar tissue.

THE PHARMACOLOGY OF ANTIBIOTICS

HANS MOLITOR*

The fact that antibiotic agents bear a common name, serve a similar purpose and originate from essentially the same type of material should not lead to the assumption that they are related chemically and pharmacologically. There is as little chemical and pharmacological relationship between tyrothricin, penicillin or streptomycin as there is between phenol, chlorine and the mercurials or between chloral hydrate, paraldehyde and the barbiturates. Nevertheless, two characteristics are common to all antibiotics. First, and above all, the chemotherapeutic activity from which the name "antibiotic" is derived; and second, the source of origin.

While the mode of chemotherapeutic action of even the best studied antibiotics is not yet too well understood (Waksman, 1947), it is clear that it materially differs from that of the so-called antiseptics or germicidal agents, *e.g.*, phenol, chlorine, heavy metals, which act largely through an irreversible destruction of microbial cells. Since this latter action equally affects the cells of the host and those of the pathogens, the usefulness of such compounds is limited to application *in vitro* or, at best, to disinfection of the skin or other exposed body tissues. In contrast to this, antibiotics seem to owe their effectiveness to an interference with vital enzyme systems of pathogenic microorganisms (Pratt and Dufrenoy, 1948) and this high degree of selectivity undoubtedly accounts not only for the amazingly low systemic toxicity of some of them, but may also be responsible for the relative ease with which microorganisms develop resistance against these agents. The prediction made in 1946 that the development of drug resistance might become the major obstacle in the use of antibiotics unfortunately has been borne out by the facts. Primary infections with penicillin and streptomycin resistant strains of certain pathogenic bacteria have been observed and the development of drug resistance in

*From the Merck Institute for Therapeutic Research, Rahway, N. J.
Presented at The University of Texas Medical Branch, Galveston, January 26, 1948.

patients is well recognized as one of the principal limiting factors in antibiotic therapy (Keefer, et al., 1946; Paine, et al., 1947).

While the phenomenon of drug resistance does not belong in a discussion of the pharmacology of antibiotics it does lend renewed importance to one of the oldest aims of pharmacotherapy: the application of Buergi's principle of drug combinations. This method, often confused with "shotgun therapy," aims at increasing the beneficial, and reducing the adverse reactions to a drug by simultaneous administration of several agents with different sites of action. Thus, in the field of chemotherapy of tuberculosis the combination of streptomycin with sulfones (Smith, et al., 1945, 1946, 1947; Callomon, et al., 1946) and para-aminosalicylic acid (Youman, et al., 1947) may prove useful; and in the therapy of certain coccal infections, simultaneous administration of streptomycin, penicillin and a sulfa-drug is likely to be superior to the use of either agent alone. If, in addition to retarding the development of drug fastness, administration of such a drug combination should also result in an overall reduction of toxic side-effects, experimental pharmacology can claim another major contribution to clinical medicine.

The second characteristic common to antibiotics is their source of origin: all are obtained from extracts of microbial cultures. Although the chemical structure of some of them has been elucidated and, indeed, a few have been synthesized in minute amounts, none are yet being synthetically produced on a large scale.

Due to their origin, antibiotics have in common certain characteristics which influence the interpretation of all experimental data: (1) When first investigated, an antibiotic usually is quite impure and its composition is neither uniform nor well-defined. (2) The method of expressing its potency is empirical and generally fails to give a complete and well-defined measure of all biological properties; potency "units" usually are based on antibiotic activity, which may or may not go parallel with the other pharmacodynamic properties. (3) Because of this, experiments performed at various times, in

various places, and with various samples of the antibiotic, are not necessarily comparable, even though the same dose, in terms of biological units, may have been used each time. The importance of this fact cannot be over-emphasized. Unfortunately it is often disregarded, even by those who are fully cognizant of its existence.

Another factor which may complicate the pharmacologic analysis of an antibiotic is the influence of a change in the medium on which the drug producing microorganisms are grown. Even apparently minor alterations, such as in the source of nitrogen or carbohydrate, may profoundly affect the pharmacodynamic effect without changing the antibacterial potency; thus Robinson, et al. (1946), found that streptothricin grown on a corn steep liquor medium produced a histamine-like fall of the blood pressure far greater than streptothricin derived from the same strain of *Streptomyces lavendulae* but grown on a tryptone medium. More recently, it has been observed in Waksman's laboratory, that the use of still another medium for the production of streptothricin yielded a preparation which had lost most of its local irritating properties. Since local irritation is observed with even the most highly purified streptothricin, Waksman's experiment would indicate that it is possible to vary intrinsic pharmacologic properties of an antibiotic without altering its bacteriological spectrum. The significance of this discovery can hardly be over-emphasized, since it opens a way for the transformation of effective but toxic antibiotics into therapeutically useful agents.

The following chart (Fig. 1) is an attempt to summarize the data pertaining to pharmacodynamic properties of some of the better known antibiotics. The information providing these data is derived from published literature. It should be emphasized that these data indicate mainly trends and are average values only. Thus, the therapeutic ratio (effective dose for 50% of the animals divided by lethal dose for 50% of the animals) depends to a large extent on the particular type and strain of microorganism used for the infection; the species; and the mode and frequency of administration of the antibiotic. Likewise, the effects upon individual organ functions vary

widely depending upon the above factors, as does the interpretation and appraisal of experimental data by the individual investigator. Results obtained at different times, in different laboratories and with materials of varying purity are therefore comparable only in the broadest, most general sense.

PHARMACOLOGIC PROPERTIES OF ANTIBIOTICS

ANTIBIOTIC	PURITY	THERAPEUTIC RATIO ED 50% / LD 50%	LOCAL REACTION	BLOOD PRESSURE	RESPIRATION	HEPATIC EFFECTS	RENAL EFFECTS	CENTRAL NERVOUS EFFECTS
TYROCIDINE	90% to 100%		±	~	DEPRESSED			
PENICILLIN G	100%	6000	–	~	NO CHANGE			I.C. ++ / S.C. –
STREPTOTHRICIN	60%	5-10	+++	V	DEPRESSED	±	+++	I.C. +++
STREPTOMYCIN	100%	340	–	~	SLIGHT DEPRESSION	–	–	I.C. +++ / S.C. +
CLAVACIN (PATULIN etc.)	100%		+++	∿	SLIGHT DEPRESSION	+	+	
PROACTINOMYCIN	80%			~	NO CHANGE	+		I.C. –(?)
BACITRACIN	10% (?)	100 (?)	±	V	NO CHANGE		+	
SUBTILIN		800-1000 (?)	+++					

Inspection of Figure 1 will immediately show the wide variations among antibiotics. Some, *e.g.*, penicillin, have an extremely low toxicity, this is in sharp contrast to that of an agent like clavacin; and between these extremes values are found which could fit almost any point on a curve. Some antibiotics are almost free from hepato- and renotoxic effects when given in therapeutic doses (penicillin, streptomycin), while the opposite is true of others (streptothricin, bacitracin). Some produce extreme local irritation (clavacin) while others exhibit this property only to a negligible degree (penicillin). In toxic doses, almost all appear to affect the central nervous system, particularly when injected directly into the cerebro spinal fluid. But here again, we find many shades of activity ranging from complete absence (penicillin) to a highly specific toxicity upon certain nervous centers, as in the case of strepto-

mycin. One characteristic, however, stands out: The great differences in the purity of the material upon which the pharmacologic data are based.

Pharmacologists and clinicians working with pure or nearly pure substances are accustomed to ascribe changes observed after administration of a drug to pharmacodynamic properties of that drug itself, except in case of allergic manifestations, (which, incidentally, are rather common with antibiotics); if however, a description of the pharmacologic properties of a new agent is based upon experiments performed with impure material, it is permissible to ask how much of the effect was due to the active principle itself and how much to impurities, particularly when their composition or chemical nature is unknown. The data shown in Figure 2 clearly demonstrate the changes which result from the continued purification of an antibiotic.

CHANGE OF PHARMACOLOGIC PROPERTIES OF STREPTOMYCIN WITH INCREASING PURITY

PURITY (approx)	L.D. 50 I.V. Units/20gm. AVERAGE	L.D. 50 S.C. Units/20gm AVERAGE	MINIMUM CIRCULATORY EFFECT Units/Kg AVERAGE	RESPIRATORY EFFECTS Units/Kg AVERAGE	PYROGENIC EFFECTS	RENAL EFFECTS	HEPATIC EFFECTS	LOCAL EFFECTS	MINIMAL CENTRAL NERVOUS EFFECTS
10%	725 (670–890)	7000	100	5000	+	+	+	+++ AT 2000 U/cc	I.C. AT 500 U/Kg S.C. 13 DAYS AT 50,000 U/Kg
25%	2200 (1750–2600)	10,000	900	15,000	±	+	+	+++ AT 20,000 U/cc	I.C. AT 1100 U/Kg
50%	2500 (2000–2920)	10,000	4000	25,000	–	+	+	+ AT 133,000 U/cc	I.C. AT 1700 U/Kg S.C. 32 DAYS AT 50,000 U/Kg
95% TO 100%	4000 (3500–4640)	25,000	25,000	NONE AT 40,000		–	–	NONE AT 133,000 U/cc	I.C. AT 2500 U/Kg S.C. 43 DAYS AT 50,000 U/Kg

The agent used in this comparison is streptomycin. It was selected not only because it is one of the most thoroughly investigated antibiotics, but also because it is pharmacodynamically sufficiently active to lend itself to a study of this nature. Furthermore, all data shown in this table were obtained in one laboratory only (Merck Institute for Therapeutic Research), and by the same group of investigators; the compli-

cating factors of varying experimental conditions and differences of interpretation therefore do not enter into the picture.

It will be noted that with increasing purity not only the doses necessary to produce certain pharmacologic effects increase sharply but also that certain effects, such as those upon kidneys and liver, disappear completely when pure material is used. The explanation for this lies in the fact that some side-effects of the early samples were entirely due to accidental impurities which could be removed, *e.g.*, the histamine-like and the pyrogenic factors. While other effects could not be so completely eliminated, their severity was greatly reduced when pure material was used.

It will also be noted that the degree of purity at which side-effects disappear varies with the organ affected. Thus, it requires only a moderately purified material to minimize the local irritating properties, while the reno- and hepatotoxic effects continue to be present until a purity of more than 95% has been obtained. It should be emphasized, however, that the doses necessary to produce these effects are far in excess of those employed clinically; for this reason a material of highest purity is not absolutely essential for safe clinical use, although it obviously is preferable.

The role played by unidentified impurities is now fully recognized and the statement is perhaps permissible that a discussion of the pharmacology of antibiotics largely revolves around that of their impurities and degradation products. Unfortunately, it is only rarely possible to use for the early pharmacological and clinical work antibiotic preparations in crystalline form or at least of high chemical purity. Intensive and costly efforts at complete purification usually have to wait until therapeutic trials with low potency material have given reasonable evidence of the practical usefulness of the new agent.

The consequences arising from this situation are two-fold: (a) Antibiotics which upon first investigation exhibit a high degree of toxicity are often discarded although it is possible that the latter may have been caused by impurities; (b) the data obtained from extensive pharmacological and clinical investigations which necessarily precede the introduction of a

new antibiotic are often based on materials of intermediate purity.

The development of a new antibiotic is an extremely costly and time-consuming undertaking and it is often not easy to create and maintain the enthusiasm of investigators (as well as sponsors) if there is not a reasonable degree of hope of arriving at something scientifically interesting and clinically useful. Furthermore, few research workers are interested in repeating already published work—either their own or that of others. Consequently, there is little inclination toward the duplication of a pharmacological and clinical investigation of an already widely used antibiotic only because the material presently available is of much greater purity than that used in previous investigations; thus, no complete pharmacologic and clinical data are yet published on the properties of pure penicillin G or pure streptomycin although both are now freely available.

Some of the impurities present in less purified antibiotics may improve the therapeutic effectiveness of the agent. Thus, it has been shown by Lewis, 1944, and Cornman, 1944, that low potency and high potency penicillins differ in their effects upon tumor growth; upon *Treponema pallidum* by Dunham, et al., 1945; *Microfilaria immitis* by the author, 1946; and certain types of virus (Groupe, et al., 1947; Eaton, et al., 1948). Recently a new factor present in varying degrees in amorphous penicillin has been discovered by Welch (1947), who termed it "enhancement factor." This factor prolongs the presence of penicillin in the blood and may thus enhance its therapeutic activity, provided that maintenance of a certain blood level is a determining factor in the clinical efficacy of penicillin. Recent papers by Jawetz (1946), Zubrod (1947) and Marshall (1947), however, do not support this assumption. Animals treated with only one or two daily penicillin doses recovered as readily as those in which a constant blood concentration was maintained by frequent injections. Similar results were reported for streptomycin (by Zubrod, 1948), in the treatment of experimental *K. pneumoniae* infections in mice. Clinical experience would seem to indicate that good results may be obtained from a

dosage regime that does not provide the maintenance of a uniform high drug concentration in the blood.

While there is little reason to doubt that crude extracts of antibiotics may contain factors capable of modifying their therapeutic activity, it is nevertheless obvious that as long as the nature of such impurities is unknown and their presence in any given lot is not standardized, such material is inferior from the viewpoint of safety of use.

While with basically non-toxic antibiotics such as penicillin an intensification of the action would not seem to be objectionable, it might be quite different with antibiotics possessing toxic properties. To the pharmacologist it would appear most desirable to identify each of the enhancement factors responsible for qualitative or quantitative changes and then add them in known amounts to a known quantity of the pure antibiotic.

A pharmacologic effect indirectly related to the antibacterial action of some antibiotics is the increase in prothrombin time noted after peroral administration. This is due presumably to an interference with the synthesis of vitamin K by intestinal bacteria. This effect has been noted clinically when streptomycin was administered preoperatively as a means of sterilizing the intestinal tract; it can be counteracted by the administration of vitamin K. Further evidence of the interference with intestinal synthesis of the vitamin has been obtained by Emerson (1945) in experimental animals fed purified diets containing streptomycin. The most pronounced symptoms resembled biotin and folic acid deficiencies, and were similar to those seen after administration of sulfa-suxidine.

Summary

The common characteristic of all antibiotics, in addition to their origin from microbial cultures, is their chemotherapeutic activity; they differ widely, however, in chemical nature and pharmacological and toxicological properties. The usual method of measuring and expressing the potency of antibiotic agents is based on their chemotherapeutic activity. This, however, does not register the possible presence of impurities or degradation products which, while not affecting the chemotherapeutic

activity, may nevertheless materially alter the pharmacologic and toxicologic properties. Pharmacological and clinical data derived from experiments with impure antibiotics may therefore vary from lot to lot quantitatively as well as qualitatively even though the materials may possess the same chemotherapeutic efficacy. Adverse side reactions following the administration of an antibiotic of low or intermediate purity may decrease or completely disappear when pure agents are used. Impurities present in antibiotics may occasionally improve their therapeutic properties. Some pharmacologic effects of antibiotics, such as prolongation of prothrombin-time, after peroral administration are indirect and nonspecific and are due to suppression of the intestinal bacterial flora. Development of drug-resistance is a frequent and serious complication of antibiotic therapy. It can largely be counteracted by the combined administration of agents with a similar therapeutic main-effect, but differing in site and mode of action.

REFERENCES

Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin. *Lancet*, *2*:177, 1941.

Anderson, H. H., Villela, G. G., Hansen, E. L., and Reed, R. K.: Some Physical and Biologic Properties of Subtilin and Other Antibiotics. *Science*, *103*:419, 1946.

Anderson, H. H., and Wong, S. C.: Antibiotics in Experimental Tuberculosis. *Tuberculology*, *8*: No. 3, 1946.

Broom, W. A., Bulbring, E., Chapman, C. J., Hampton, J. W., Thomson, A. M., Ungar, J., Wien, R., and Woolfe, G.: The Pharmacology of Patulin. *Brit. J. Exp. Path.*, *25*:195, 1944.

Callomon, F. T., Kolmer, J. A., Rule, A. M., and Paul, A. J.: Streptomycin and Diasone in the Treatment of Experimental Tuberculosis of Guinea Pigs. *Proc. Soc. Exp. Biol. and Med.*, *63*:237, 1946.

Cornman, I.: Survival of Normal Cells in Penicillin Solutions Lethal to Malignant Cells. *J. Gen. Phys.*, *28*:113, 1944.

Dunham, W. B., and Rake, G.: The Relative Activity of Partially Purified Penicillin and of Crystalline Penicillin G on *Treponema pallidum*. *Am. J. Syph., Gonor. and Ven. Dis.*, *29*:214, 1945.

Eaton, M. D., Dozois, T. F., VanAllen, A., Parish, V. L., and Schwalin, S.: Studies of Inhibition of the Agents of Murine and Feline Pneumonitis by Penicillin. *J. Immun.*, *58*:251, 1948.

Emerson, G. A., and Smith, D. G.: Induction of Nutritional Deficiency by Oral Administration of Streptomycin. *J. Pharm. and Exp. Therap.*, *85*:336, 1945.

Florey, H. W., Jennings, M. A., and Sanders, A. G.: Biological Investigations on Proactinomycin. *Brit. J. Exp. Path.*, *26*:337, 1945.

Groupe, V., and Rake, G.: Studies on the Chemotherapy of the Pox viruses. *J. Immun.*, *57*:17, 1947.

Jawetz, E.: Dynamics of the Action of Penicillin in Experimental Animals. *Arch. Int. Med.*, *77*:1, 1946.

Johnson, B. A., Anker, H., and Meleney, F. L.: Bacitracin: A New Antibiotic Produced by a Member of the B. subtilis Group. *Science, 102*:376, 1945.

Keefer, C. S., Blake, F. G., Lockwood, J. S., Long, P. H., Marshall, E. K., and Wood, W. B.: Streptomycin in the Treatment of Infections. *J.A.M.A.*, *132*:70, 1946.

Kiser, J. S., and Zellat, J. S.: Antibiotics, Other Than Penicillin, Produced by Penicillin. *Trans. N. Y. Acad. Sci.*, *7*:210, 1945.

Lewis, M. R.: The Failure of Purified Penicillin to Retard the Growth of Grafts of Sarcoma in Mice. *Science*, *100*:314, 1944.

Marshall, E. K.: *The dosage schedule of Penicillin.* Antibiotic Study Section Seminar, National Institute of Health. 1947.

Molitor, H.: Bacterial Chemotherapy. *Fed. Proc.*, 5:304, 1946.

Molitor, H.: The Pharmacology of Streptothricin and Streptomycin. *N. Y. Acad. Sci.*, *48*:101, 1946.

Molitor, H.: Pharmacology of Streptomycin. *Bull. N. Y. Acad. Med.*, *23*:196, 1947.

Molitor, H., Graessle, O. E., Kuna, S., Mushett, C. W., and Silber, R. H.: Some Toxicological and Pharmacological Properties of Streptomycin. *J. Pharm. and Exp. Therap.*, *86*:151, 1946.

Molitor, H., and Kuna, S.: The Significance of Neurotropic Properties of Commercial Streptomycin. *Arch. Intern. Pharmacodyn. et Therapie, 74*:334, 1947.

Mushett, C. W., and Martland, H. S.: Pathologic Changes Resulting from the Administration of Streptomycin. *Arch. Path.*, *42*:619, 1946.

Paine, T. F., Murray, R., and Finland, M.: Streptomycin II. Clinical Uses. *New Eng. J. Med.*, *236*:748, 1947.

Pratt, R. and Dufrenoy, J. Cytochemical Interpretation of the Mechanism of Penicillin Action. *Bact. Rev. 12*:79, 1948.

Rake, G., Hamre, D., Kavanagh, F., Koerber, W. L., and Donovick, R.: On the Toxicity of Streptothricin. *Am. J. Med. Sci.*, *210*:61, 1945.

Robinson, H. J.: *Some Toxicological, Bacteriological, and Pharmacological Properties of Antimicrobial Agents Produced by Soil Micro-organisms.* Thesis for Doctor of Philosophy, Rutgers University, 1943.

Robinson, H. J., Graessle, O. E., Gundel, M., and Silber, R. H.: Pharmacological Studies on Streptothricin. *J. Pharm. and Exp. Therap.*, *86*:22, 1946.

Robinson, H. J., and Molitor, H.: Some Toxicological and Pharmacological Properties of Gramicidin, Tyrocidine and Tyrothricin. *J. Pharm. and Exp. Therap.*, *74*:75, 1942.

Scudi, J. V., and Antopol, W.: Some Pharmacological Characteristics of Bacitracin. *Proc. Soc. Exp. Biol. and Med.*, *64*:503, 1947.

Scudi, J. V., Clift, M. E., and Krueger, R. A.: Some Pharmacological Characteristics of Bacitracin II. Absorption and Excretion of Bacitracin in the Dog. *Proc. Soc. Exp. Biol. and Med.*, *65*:9, 1947.

Smith, M. I., and McClosky, W. T.: The Chemotherapeutic Action of Streptomycin and Promin in Experimental Tuberculosis. *Pub. Health Rep.*, *60*:1129, 1945.

Smith, M. I., McClosky, W. T., and Emmart, E. W.: The Influence of Streptomycin and Promin on the Proliferation of Tubercle bacilli in the Tissues of the Albino Rat. *Fed. Proc.*, 5:204, 1946.

Smith, M. I., McClosky, W. T., and Emmart, E. W.: Influence of Streptomycin and Promin on Proliferation of Tubercle bacilli in the Tissues of Albino Rat. *Proc. Soc. Exp. Biol. and Med.*, *62*:157, 1946.

Smith, M. I., McClosky, W. T., and Jackson, E. L.: Studies in Chemotherapy of Tuberculosis. VIII. The Comparative Action of Four Sulfones in Experimental Tuberculosis in Guinea Pigs and the Combined Action of Streptomycin with one of the sulfones. *Am. Rev. Tuberc.*, *55*:366, 1947.

Smith, M. I., McClosky, W. T., Jackson, E. L., and Bauer, H.: Chemotherapeutic Action of Streptomycin and of Streptomycin with a Sulfone or Sulfadiazine on Tuberculosis. *Proc. Soc. Exp. Biol. and Med.*, *64*:261, 1947.

Smith, M. I., McClosky, W. T., Jackson, E. L., and Bauer, H.: The Chemotherapeutic Action of Streptomycin and Sulfone Derivatives in Experimental Tuberculosis. *Fed. Proc.*, *6*:372, 1947.

Stanfeld, J. M., Francis, A. E., and Stuart-Harris, C. H.: Laboratory and Clinical Trials of Patulin. *Lancet*, *2*:370, 1944.

Waksman, S.: *Microbial Antagonisms and Antibiotic Substances.* The Commonwealth Fund, 1947.

Waksman, S. A., and Hutchison, D.: Personal communication. 1947.

Welch, H., Randall, W. A., and Price, C. W.: The Demonstration in Amorphous Penicillin of a Non-penicillin Factor Which Enhances its Protective Action. *J. Am. Pharm. Assn.*, *36*:337, 1947.

Youmans, G. P., Youmans, A. S., and Osborne, R. R.: The Combined Effect of Streptomycin and Para-aminosalicylic acid on Experimental Tuberculosis in Mice. *Lancet*, *67*:403, 1947.

Zubrod, C. G.: Relation of Dosage Schedule to Therapeutic Efficiency of Streptomycin in the Treatment of K. pneumoniae Infections in Mice. *Bull. Johns Hopkins Hosp.*, *82*:357, 1948.

Zubrod, C. G.: Comparative Efficiency of Single and Multiple Dosage Regimens of the Penicillins. *Bull. Johns Hopkins Hosp.*, *81*:400, 1947.

THE NEED FOR PHYSICAL MEDICINE REHABILITATION IN GENERAL PRACTICE AS INDICATED BY THE EXPERIENCE OF THE VETERANS ADMINISTRATION

A. B. C. KNUDSON*

The Physical Medicine Rehabilitation Service was established in the Department of Medicine and Surgery of the Veterans Administration in order to restore every sick and disabled veteran to his former physical and mental status in the shortest possible time, thus reducing the period of hospitalization, and returning the veteran to his community able to compete with his fellow-citizen physically, mentally, socially and economically. In fact, in many instances he has been restored to a level superior to that possessed by him prior to his illness or injury.

After observation of a comprehensive rehabilitation service in the VA for over two years, we propose the thesis that physical medicine rehabilitation is needed in general practice today more than ever before. Rehabilitation problems of the veteran cannot be discussed without taking into consideration the medical problems of the Nation—and this involves the general practice of medicine. It is our firm belief that there are no limits to what free American medical ingenuity can provide for a more profitable way of life for the Nation's handicapped.

We feel that a proper appreciation of the therapeutic benefits to be derived from physical medicine rehabilitation in traumatic injuries and various disease conditions has not yet been widely disseminated throughout the medical profession as a whole, although the variety of traumatic conditions which arose in World War II, and the service in the Armed Forces of such a large number of physicians in rehabilitation work has done much to distribute modern ideas and concepts of physical medicine rehabilitation.

*Assistant Chief, Physical Medicine Division, Physical Medicine Rehabilitation Service, Department of Medicine and Surgery, Veterans Administration, Washington, D. C. Presented at the Third Postgraduate Course in Physical Medicine and Medical Rehabilitation, The University of Texas Medical School, Galveston, Texas, March 2, 1948.

The Veterans Administration believes in the dynamic rehabilitation of the disabled veteran and his effective employment following his restoration to usefulness. We insist that physical medicine rehabilitation in the Veterans Administration must be an individualized therapy and that we make every part of the program purposeful for the eventual independence of the veteran.

Likewise, in general practice, the burden of translating to the patient the nature and extent of his disability falls upon the family doctor. That explanation cannot be in medical terms of the disability alone, but must be in terms of its effect on the vocational, social, economic, family and personal life of the patient. This must be done by the doctor and must be predicated on an accurate knowledge of what can be done for the patient.

It is almost unbelievable that such phenomenal progress in American medicine as we have all witnessed could leave unhelped and still hopeless, thousands and thousands of disabled, deformed and chronically ill individuals. When we became too interested in the etiology and diagnosis of disease, we gradually lost sight of the human side of medicine as affecting each medical and surgical patient. When the postoperative period was at an end, or after the temperature in a case of pneumonia had been normal, for a time, the patient was allowed to go home, and from that point his future progress and welfare was guided by his own thinking, the advice of neighbors, and economic pressure for the needs of living. But even worse than such instances are those thousands of unfortunate, but potentially rehabilitatable persons, who were born disabled or received a serious disability through accident or as a residual of disease. Families are often sensitive about such afflicted members of the household, and they frequently hide them away, so to speak, from the progress and contacts of the outside world.

Thus the need for medical rehabilitation in every community to take care of the current load of patients passing from the definitive to the convalescent stages of their illness or injury, as well as to restore as much as possible the back-log of forgotten humanity, is most obvious. However, it may be pointed out by

the experience of the Veterans Administration that even though this need is urgent and comprehensive, the problem is not insurmountable nor even as formidable as it appears. The need for physical medicine rehabilitation covers every field of medicine from pediatrics and orthopedics to neurology and geriatrics. Time will not permit a complete coverage of all the possibilities in these and other fields, but a few typical comparisons will be made.

Opinion has been expressed that most war-time injuries and illnesses are no different from those encountered in everyday practice, or at least are closely correlated with them. This is true, for example, in the etiology of war neuroses, referred to as "shell-shock" in the first World War; and in the case of paraplegia in World War II. It has been shown that paraplegics discharged from VA Hospitals are replaced by other paraplegics injured in civilian life in plane and car accidents, diving and by falls from scaffolds, elevator shafts and the like. You are all familiar with the figures of approximately 17,000 amputations done in the Army during the first four years of World War II, but during the same period there were 120,000 major amputations from disease and accident in the civilian population.

Overshadowing these figures and making the case for widespread community rehabilitation in general practice even more necessary is the distinct progressive upsurge in cutting down bed rest. The now widely used early ambulation in surgical and medical conditions makes it imperative that a properly supervised and medically guided program take these people from the completion of definitive care through the "third phase of medicine" until they are ready to resume full-time employment.

The Veterans Administration has established complete medical rehabilitation programs in all of its 126 hospitals, these being classified as General Medical and Surgical, Neuropsychiatric, Tuberculosis, Paraplegic Centers, and Rehabilitation Hospitals. In addition, all available technics in rehabilitation are available in many Veterans Administration Regional Offices which function medically in a manner similar to out-

patient clinics. The first Veterans Administration Rehabilitation Hospital was opened at Fort Thomas, Kentucky, last September (1947) and receives hospitalized veterans screened from other Veterans Administration Hospitals throughout the country for the final stages of their complete restoration to society and employment. There are approximately eighty physiatrists in Veterans Administration Hospitals who serve as Chiefs of the Physical Medicine Rehabilitation Service in the hospital and as Chairmen of Medical Rehabilitation Boards which function as specialized steering committees for guiding the more severely disabled patients to a completion of their rehabilitation cycle.

Since the inauguration of the Medical Rehabilitation Service in 1945 by General Bradley and Dr. Hawley, and the appointment of Dr. Donald A. Covalt to head this project, far-reaching strides have been made in rehabilitation for all types of disability and disease. In November, 1947, Dr. Covalt resigned his position with the Veterans Administration in order to become associated with Dr. Howard A. Rusk in New York City in further developing civilian rehabilitation. Dr. Covalt now serves us as Special Consultant in Medical Rehabilitation. Dr. A. Ray Dawson, who was associated with Dr. Rusk and Dr. Covalt in the Army Air Forces during World War II, was Chief of Physical Medicine Rehabilitation in Veterans Administration Branch Office, Richmond, Virginia, until November, 1947, when he succeeded Dr. Covalt as Assistant Medical Director for Physical Medicine Rehabilitation. This service has progressed very rapidly because of the large amount of clinical material available in Veterans Administration hospitals, and in turn, the excellent results achieved have been a stimulus for further development. Amputees, paraplegics, arthritics, cardiacs, hemiplegics and others have been helped. The Physical Medicine Rehabilitation Service has been utilized throughout the neuropsychiatric program both in the acute and chronic stages of mental disease. In the latter phase, *i.e.*, in chronic psychosis, medical rehabilitation has been looked upon as one of the main therapies for the motivation improvement and socialization of these men. In tuberculosis new hope has been

given the tuberculous veterans, so they are satisfied to remain in the hospital until their treatment period is completed. They are retained for new vocations if same is indicated so they will not break down or have to be readmitted. You are all familiar with the progress made in the rehabilitation of the paraplegics. You have heard how they died shortly after their injuries in World War I; one and one-half to two years being the maximum life expectancy. They were saved in this war by improved methods in medicine, surgery, and urology for what? To lie in bed the rest of their lives? On the contrary, the majority of them are healthy, robust looking specimens of young manhood, and upon discharge they are able to cope with street traffic, drive their own cars, fly planes, swim and to work at a vocation for which they were advised and guided while in the hospital.

Hemiplegia is a condition of such great importance in general practice and is becoming of increasing significance in the Veterans Administration. With the increase of average age for veterans of all wars the incidence of hemiplegia among veterans is very similar to the rate found in civilian practice. Through modern methods of rehabilitation they are not doomed to a rocking chair existence upon returning to their homes from the hospital, but are able to be active, to perform self-care, and, in many instances, to participate in part or full-time employment.

It has been estimated that 50,000 epileptic veterans will require study and treatment in the next 10 years. Among the casualties of World War II, there are about 20,000 craniocerebral injuries, about 2400 paraplegics, and 600 post-traumatic aphasic patients. As time goes on and veterans become older and hence more vulnerable to neurologic insults the number will steadily increase. For example, the peak of the neurological census from World War I is not expected to be reached until 1949.

The Veterans Administration Physical Medicine Rehabilitation Service has made notable contributions to rehabilitative medical procedure, proven by the interest of civilian hospitals and clinics of this and foreign countries in this phase of Veterans Administration medicine. As each year yields richer

and more significant returns, this in itself imposes the obligation of effecting continued improvement in physical medicine rehabilitation techniques. We are making the fullest opportunity of these results in our current operation as well as in future planning.

The experience of the Veterans Administration has shown that physical medicine is an integral part of the necessary treatment that should be provided by modern medical practice. The demand for this service is increasing.

We have proven in the Veterans Administration that where an adequate and complete Physical Medicine Rehabilitation Service is provided, four important accomplishments result: (1) the patient days of hospitalization are reduced; (2) residuals of injury or sickness are lowered; (3) the patient is assisted to a more satisfactory social and economic adjustment compatible with his disabilities and (4) readmissions are fewer.

The adaptation of such technics to general practice deserves serious consideration because of the opportunities in this field in conjunction with labor and industry. The large number of veterans in the population who have been hospitalized know the possibilities when rehabilitation is a part of the medical program; they will demand the same services from the civilian medical profession for their families and neighbors. The inauguration of rehabilitation services in every community should be looked upon with encouragement and enthusiasm, because of the tremendous bearing it would have on the social life and prosperity of this country.

The increasing age of our population, the saving of war casualties, the decreasing mortality in children, and the improvements in medical and surgical methods all point to such a need.

Physical medicine rehabilitation in the Veterans Administration includes all the accepted technics of physical medicine, which are used in the preventive, diagnostic, therapeutic and rehabilitative objectives of treatment and restoration of the sick and disabled. It is realized that in the rural areas and small communities so common to the general practitioner there is often no physical medicine department or rehabilitation clinic available for his own use or for his referral. However,

we are convinced that the need for these measures is more vital in these areas than in many of our larger cities where we do find complete departments with a physiatrist in charge of the clinic, and where it is merely necessary to refer the patient to be assured of his proper treatment with the measures available in this specialty. In the Veterans Administration we have made use of the ideas of America's leaders in physical medicine in the development of our rehabilitation program, and which we feel is adaptable for community planning, and which we hope will become a part of our communities for better living.

The Baruch Committee on Physical Medicine after a careful survey found that: "There is a great need for a community rehabilitation service and center program to provide the necessary care and rehabilitation for the estimated 23,000,000 persons in the United States who are handicapped because of disease, injury, maladjustment, or from former wars." Dr. George G. Deaver, Consultant to the Veterans Administration in Medical Rehabilitation, stated, "Rehabilitation is a service and right that must be made available to citizens in a democracy and they have a right to expect such opportunities."

Dr. George M. Piersol, Branch Consultant to the Veterans Administration in Physical Medicine, has stressed the vital importance of physical procedures and the need for better cooperation between physiatrists and general practitioners. "Most physicians have failed to take much interest in this branch of medicine, owing to lack of information on the subject. Too many practitioners think of physical medicine as consisting of little besides heat and massage and do not have a clear idea of what can be done or what needs to be done when they refer a patient."

I shall read an actual letter written to a Minnesota physician by a layman which illustrates the above patient with reference to inadequate education of the public regarding physical medicine.

"Dear Sir· Seeing the write up in the Mpls. Sunday Tribune about the Physical Medicine for people thats paralized for different diseases and even those that have arthritis. Well thats my trouble, for I sure would like to find some relief for

it, as I have it in my left hip. So Doc, if you think that Physical Medicine will help me, I wish that you would send me some and I sure will give it a trial . . . Either send it C. O. D., or I can mail you a check for it, after I received your medicine."

Dr. Frank H. Krusen, National Consultant to the Veterans Administration in Physical Medicine, has observed that, "It probably would be wise for the average medical practitioner to get 'up on' the subject of physical medicine because for an extensive group of patients physical measures can be employed advantageously." This he is putting into action, since the first course, "Physical Medicine for the Internist" sponsored by the American College of Physicians, will be held at the Mayo Clinic under Dr. Krusen's direction from March 22 to 26, 1948, inclusive.

It should be emphasized that it is widely believed that effective physical medicine procedures require the use of complicated and expensive apparatus, but this is incorrect. The knowledge persists however because of the omission or negligence of teaching physical medicine in our medical schools in the past. Today, many of our schools of medicine have a department with a well qualified physiatrist in charge. A recent addition to these schools of medicine is George Washington University School of Medicine, Washington, D. C., to which Dr. Charles S. Wise has recently come from a three year Baruch Fellowship at Harvard Medical School and the Massachusetts General Hospital. Many schools less fortunate are looking about for a man to establish such a unit. Many procedures in physical medicine are comparatively simple procedures which require no elaborate equipment and are readily adaptable for use both in the office and in the home; however, qualified personnel are needed, both for the treatment in the hospital or clinic and for proper instructions for the patient to carry out at home. Dr. Krusen has repeatedly emphasized this phase of treatment, and the Mayo Clinic gives instructions for home care to their patients.

However, as Piersol points out, the successful use of physiatric methods in practice depends on the physician doing his part, such as: (1) making the correct diagnosis; (2) familiarity with the technics offered by physical medicine; (3) having a

thorough understanding of the physiologic reactions which these procedures bring about in the body as a whole as well as locally and (4) possessing technical skill and manual dexterity essential to proper administration of the indicated treatments or teaching of these to the patient.

Piersol elaborates further on this point, "Physicians, as a rule, because of their lack of understanding, evince little interest in acquiring a sound working knowledge of physical medicine. Furthermore, the proper application of physical therapeutic methods requires not only time but a certain amount of manual dexterity. Since physicians have been loath to give of the former or to acquire the latter, the field of physical medicine has been neglected by the medical profession." We invite general practitioners to take a dynamic professional interest in physical medicine rehabilitation and its adaptability to general practice.

What are some of the needs of physical medicine rehabilitation in general practice?

First, let us consider farm accidents, which, on account of more modern and mechanized machinery for every farm task, are increasing each year. Many of these traumatic accidents are severe and most injurious to the deeper tissues, with bone fractures, nerve injury and laceration of vessels and ligaments. The Mayo Clinic at Rochester, Minnesota, has revealed recently the results of a nine-year study of farm accidents. Causes of the injuries included falls from machinery, vehicles, haymows, ladders, trees and buildings, pitchfork wounds, machine accidents, livestock accidents and burns. The results were similar to those of fighting men in combat—paralysis, third-degree burns, amputations and fractures. Dr. Howard A. Rusk, National Consultant to the Veterans Administration in Medical Rehabilitation, stated that according to the National Safety Council, the accidental death total of farm residents in 1945 was 16,000 or almost four times the number of American deaths in the bloody twenty-six day assault of Iwo Jima. Farming is now the most hazardous of the seven major industrial groups. There was an eight per cent increase in accidental farm deaths in 1945 over 1944. Rusk states further that today forty per cent of the counties in the United States, with an

aggregate population of 15,000,000 do not have a single approved hospital. "The farmer who is hurt in a tractor accident, gored by a bull, or pierced by a pitchfork tine usually needs immediate hospital care. Often these facilities are not immediately available in many of our rural areas." In like manner the technics of physical medicine rehabilitation are required for the complete recovery and reintegration of these farmers back to their jobs. This is further shown in a study by the Farm Security Administration in 1940 which showed a higher incidence of physical disabilities among farmers than among urban dwellers. Rusk points out that, compared with the overall Selective Service rejection rate of 43 per cent, the rate for farmers was 53.4. "Farm youths in the 18–19 year old group were rejected for physical defects at a rate of 40 per cent higher than for all others. Many of these defects could have been remedied if the proper medical attention and rehabilitation opportunities had been available."

Outside of the Veterans Administration—it must be emphasized that there are large numbers of individuals who are disabled today, not as a result of military service, but as a result of farm, industrial, home and automobile accidents. Just as veterans are given the services of physical medicine rehabilitation in Veterans Administration hospitals so civilians should have a place for complete care. The first postwar year, 1946, witnessed an increase of about 3000 in the number of deaths resulting from accidents of all kinds. The accident toll in the United States in 1946 was approximately 99,000 lives, as compared with about 96,000 in 1945. This was largely due to an increase in the number of deaths from motor vehicle accidents. In addition, there were increases in the number of home accidents and public accidents not involving a motor vehicle.

For example, it has been estimated that accidents occurring in and about the American home claim around 32,000 lives a year and of the victims, some 24,000 are adults. There has been a sharp rise in the number of persons killed or injured in automobile-bicycle collisions. Fatal accidents in this country vary between 50 and 200 annually per 100,000 of population. Disabling nonfatal injuries, however, may run as high as 100

times the fatalities! Thus rehabilitation of non-fatal accident victims is an important part of our medical responsibility.

Each year several thousand disabling accidents happen in the home. For example, the kitchen alone is very often a combination factory, bakery, cannery, laundry, butcher shop, restaurant and general household workshop, not to mention recreational area. In industry, where similar hazards are present, there are specific individuals to look after accident possibilities and to adopt preventive measures. But in the home this job is just a family responsibility and so the accidents keep on occurring.

The matter of rehabilitating all housewives who have chronic illnesses and major disabilities is a tremendous rehabilitation problem which deserves careful research and appropriate measures for its solution. Accomplishment of this rehabilitation problem would perform untold benefits in greater contributions to community as well as to family life in making happier, more efficiently operated homes.

We know that the automobile, so common in this country, is causing severe crippling accidents daily on our highways in an ever-increasing number. Factories throughout the country are installing and operating more complicated and faster machinery to speed up production. The airplane has become common personal property; almost each day we can pick up the paper and read of a crash involving spinal injuries and other severe trauma. I am sure that we all realize the march of these events, but when we are so busy in everyday practice we often do not pause to get a realization of the scope of these traumatic tragedies and their effect upon the citizens of our communities, and for the need of a full therapeutic regime in their treatment, including physical medicine rehabilitation, the "third phase of medicine." Although the First World War developed physical therapy as a definite part of medical treatment, it was World War II, with its greater areas of combat and the highly mechanized death-dealing implements of battle, that really allowed physical medicine rehabilitation as a specialty to prove its need and usefulness.

The remarkable advances made during World War II in physical medicine and medical rehabilitation were continued

in the Veterans Administration. The techniques are now paying huge dividends in the saving of lives and in the restoration of disabled veterans to social and economic adjustment. These dividends should increase many fold during the next ten years due to investigations and research projects in this specialty now under way in the Veterans Administration and in civilian institutions. Standard criteria have already been developed for the attainment of essential activities in daily living by disabled individuals so that they can care for themselves, get to and from the job and do a day's work.

In the field of research, hospitalized patients in Veterans Administration hospitals present an enormous amount of clinical and statistical data for investigative purposes, which can be used advantageously by civilian, industrial and government medical groups. This is especially true in physical medicine rehabilitation for in this sphere lie many problems to be solved. We all share the responsibility for the solution of these problems.

In the field of industrial medicine, physical medicine has played a very important part and will continue to play even a more vital role because of the large scale development in all types of industry with more complicated and faster revolving machinery. Even before the beginning of World War II industrial management and industrial physicians were impressed with the aid which physical medicine could render them in their field, and as a result of this increasing need for the services and benefits provided by the physiatrist, many industrial plants have established an efficient physical medicine service as an integral part of their medical set-up.

In general practice one does everything possible in emergency treatment and definitive care to save the lives of injured accident victims. Deaver asks, "Of what use is it to save the body if it cannot function mentally, socially, or vocationally in the world in which it lives? What are the essential activities necessary to become physically, mentally, socially, vocationally, and economically useful? We have found the essential activities to be (1) walking and traveling, (2) caring for daily needs and (3) using the hands in the performance of specific activities. Superior intelligence and skillful hands are of no voca-

tional value unless the person is able to travel to a place of business to use his mind and hands."

Physical medicine rehabilitation thus becomes the doctor's responsibility. General practitioners can safeguard the best interests of their patients by availing themselves of these proven methods and techniques. When the family doctor refers the patient to a physiatrist he should follow the case with him, and should give his opinion at times when the physiatrist thinks a change of treatment is indicated. This close co-operation and understanding on a team-work basis between the practitioner and the physiatrist are necessary if the larger number of patients who need physical medicine rehabilitation are going to receive the most effective treatment. In communities where there is no physiatrist, the general practitioner must be willing to take over this additional responsibility just as he performs the duties of the obstetrician or the dermatologist. Short, intensive courses in physical medicine, as the one I mentioned to be given at the Mayo Clinic, and this one at The University of Texas, will make him more qualified and understanding of the needs of the patient along these lines.

In illustrating just a few instances where methods of physical medicine rehabilitation are useful in general practice, I must mention that the field of geriatrics is one which should be of intense interest just as it is to us in the Veterans Administration. Geriatrics is becoming an important specialty of medicine because of the changing characteristics of our population. The conditions which afflict ageing patients offer especially favorable opportunities for the application of physical agents in treatment. Kovacs stated, "The principal systemic changes in old age are the wearing out of tissues through vital processes, and the increasing difficulty of anatomical and functional restitution without real pathological changes. These and other irreversible changes call for conservative methods of treatment such as are offered by physical agents. Physical measures improve function and counteract the progress of disease processes. The benefits of these agents on conditions of old age are instinctively recognized by animals and men: the old dog lies in the sun and takes a sun bath; old people love to sit in the sun, especially on cold days. It is said of King David in the Book of Kings: "Now King

David was old and stricken in years, but he got no heat. Wherefore his servants said unto him, 'Let there be sought for my lord the King a young virgin; and let her stand before the king, and let her cherish him, and let her lie in thy bosom, that my lord the king may get heat."

We in the Veterans Administration have given a great deal of attention to the matter of medical care and related rehabilitation activities for aged veterans. The average World War I veteran is now 55 years of age and the average World War II veteran is almost 30 years old. In the next ten to fifteen years, veterans as a whole will constitute an age group which will demand special measures if they are to live useful lives. Contrary to general concepts, many disabled men and women in the more advanced age groups can be rehabilitated to the point of leading useful lives and holding down productive jobs once more.

The ageing of our population has been a matter of increasing interest to medicine in recent years. The proportion of people 65 years and older has jumped from 4.1 to 6.8 per cent between 1900 and 1940, and it is estimated that it will exceed 13 per cent before the end of the present century. Thus this must become an important consideration in our medical thinking and planning. It has been estimated that 70 per cent of persons permanently disabled are at the ages 45 or higher. We, as doctors and therapists, must meet this challenge—and at the same time a great opportunity exists for very substantial accomplishment in this field. By utilization of rehabilitation methods we will not only add years to the expectancy of life, but also increase the productive capacity of the country as a whole.

A significant aspect of this phase is the longevity of the wage-earner. The wage-earners are the backbone of our Nation and of medical practice. According to Metropolitan Life statistics, "The average length of life in our industrial population has increased by five years in the decade since 1936, and by more than ten years in the two decades since 1926. The improvement in prevention of accident and disease and of treatment has added practically 19 years to the average length of life of this important segment of our population."

I will mention briefly the disease, poliomyelitis, which remains unusually prevalent from year to year. However, the trend of mortality from this disease has been downward over the past 35 years. Throughout the years physicians have increased their ability to diagnose the disease and there have been many improvements in the method of treatment—thus saving more lives to be rehabilitated if they are to be again useful to society. Poliomyelitis is the greatest single cause of crippling in childhood, and is responsible for almost one-fifth of all orthopedic handicaps at ages under 21.

What is the economic loss to our country of the inability of disabled individuals to work? Personal injuries and disease resulting in permanent impairments take a very heavy toll annually, not only in human suffering, but also in loss of productive capacity. Each year about one-third of a million persons in the United States become permanently impaired, either partially or totally, through accidental injury alone. The magnitude of these losses is stressed to point out the importance of adequate rehabilitation in every community to put the disabled man back in a gainful occupation. Large as these losses to individuals may be, their full import is realized only by considering their aggregate over the whole Nation.

Dr. Howard A. Rusk compiled the following figures:

1. One person out of every twenty is disabled by sickness or accident in any twenty-four hour period.
2. 25,000,000 suffer from chronic ailments, many of which are disabling.
3. 1,000,000 deaths occur yearly from chronic disease.
4. 10,000,000 days of disability each year result from chronic disease.
5. Those suffering disabilities from accidents number over 10,000,000; mental diseases 8,000,000; diseases of heart and arteries 6,850,000.

Dr. Rusk states that the economic problems connected with these figures are:

1. About 97,000,000 people in the United States need financial help to meet the cost of serious illness. This averages two persons out of three.

2. The estimated annual cost of sickness and accidents in loss of earnings due to sickness and premature death is $8,000,000,000.
3. The total hidden costs of sickness and disability, wage loss to workers and costs to industry totaled more than $15,000,000,000 in 1943.

It has been proven that rehabilitation pays off economically! In our Veterans Administration Hospitals we have shown that physical medicine rehabilitation is economically sound and has actually saved the Government thousands of dollars. In planned rehabilitation centers in smaller communities part-time rehabilitation assistants can make valuable contributions to the basic planning of the physician. The athletic director in the school, vocational teachers and other trained persons in the community can be organized to do a functional team job on a part-time basis, working under the direction of the doctor to give a limited but most valuable rehabilitation program until full-time employees can be made available.

Disabled civilians should be given the same opportunities for rehabilitation as are provided for disabled veterans and which have proven to be economically and socially sound. United, we must take positive steps to provide these opportunities. Some 350,000 citizens of the United States joined the ranks of America's permanently disabled from accidents in the year just past (1947). In addition there are 7,000,000 who suffer from arthritis, 1,000,000 who have serious speech disorders, 200,000 with cerebral palsy; and other millions with heart disease, tuberculosis, loss of sight, loss of hearing, diabetes and other diseases; altogether a staggering total. Rusk has stated that, with but few exceptions, those maimed in battle and those disabled by accidents and disease in civilian life must overcome the same handicaps. "It is agreed and must be followed that rehabilitation is a common problem to be shared by all citizens, whether disabled or ablebodied, whether veteran or civilian. Rehabilitation cannot be done in segments." It falls upon the general practitioner to take the lead in general practice in providing proper medical supervision in this huge task.

Do the disabled live up to employment standards following their rehabilitation to a job? Rusk states, "Through their courage and fortitude in overcoming handicaps, disabled persons have earned our respect and admiration as individuals; and, by their ability, perseverance and loyalty, they have proved their worth as employees. It is our duty, as members of a democracy, to provide—not charity, nor pity, nor privilege—but equal opportunity to compete for social and economic security."

It is interesting to note at this point that during the war 83 per cent of our Nation's industries employed handicapped workers. These industries report that among the handicapped there was a much smaller turnover, less absenteeism, fewer accidents and equal or higher production rates. Rehabilitation is therefore no longer merely an interesting experiment. It has come of age as a necessary part of our medical thinking, and is a great field in the specialty of physical medicine. It has been estimated that up to 97 per cent of all our handicapped can be rehabilitated to such an extent that they can be gainfully employed. The answer to the utilization of these handicapped workers lies not so much in fitting the job to the worker as in fitting the worker to the job. It is a matter of proper placement. It is a great opportunity for the general practitioner, but if he is to meet the needs of his patients in this respect, he must know something about physical medicine rehabilitation and also selective placement following rehabilitation.

Likewise, civilian hospitals can be made into institutions of opportunity. You will hear more on this from Dr. Frank H. Krusen in his talk on "Rehabilitation in Civilian Hospitals." I would like to point out, however, that it has been shown that the average person in the hospital suffers but 10 per cent of the time and is bored to death, the other ninety per cent of the time. Let the hospital take its place in the community with programs for rehabilitating the patients and to aid in their orientation back to normal living. Hospital time should be made purposeful instead of tedious. Qualified volunteers can be obtained to do the teaching under the supervision of the hospital medical and administrative staff. If the average stay in the hospital is cut in half, it follows that this fact can at least double the

capacity of hospitals to care for surgical patients and thus actually increase their revenues. It has been demonstrated through planned convalescence, stressing activity as adjunctive therapy, and through rehabilitation, that hospital readmission rates can be reduced and the period of hospitalization shortened. Such a program would relieve some of the pressure of the need for acute beds and permit some of the planned hospital construction to be replaced by rehabilitation and convalescent facilities that would be less expensive to construct and maintain.

The Baruch Committee on Physical Medicine found that the average cost per patient was about $4.13 per patient per day in a rehabilitation center. It was estimated that administrative and professional costs for a comprehensive rehabilitation center for 250 patients with an average stay of two months would be approximately $2.00 per patient per day. Add these two figures together and the total is still far below the average patient-day cost for definitive medical care.

Either we must finish the task of rehabilitation for the whole country in the light of the new accomplishments in the third phase of medicine, or we must reconcile ourselves to seeing military and veteran rehabilitation overshadowed by the larger civilian problem, which would be consistent neither with good judgment nor with the steady progress made so far in this specialty. In the last analysis the eventual solution to this tremendous problem can in largest measure only come from the general practitioner who has by his ingenuity over the years already set the standard for victory over other obstacles equally as great.

Thus, it becomes more and more necessary for every practitioner to be familiar with the therapeutic principles of physical medicine rehabilitation, because physical agents are particularly useful in the modern management of disease, and rehabilitation is necessary following definitive care until the patient is back to his home, reintegrated into his community, and ably performing his job. If we have been able, in our efforts, to stimulate the thinking and the interest of general practitioners, we are grateful—for it is true that enlightened general practitioners are the best means to quicken progress in rehabilitation for the common benefit of our country's disabled.

I desire to make a strenuous plea for better understanding and more extensive employment of these measures by general practitioners. Such a step will be of untold benefit to humanity in every community of general practice in our Nation!

REFERENCES

Baruch Committee on Physical Medicine: Report of—Pamphlet, 24 pp. 1946.

Covalt, Donald A.: The Medical Rehabilitation Program in the Veterans Administration, Occupational Therapy and Rehabilitation, 25: 1 (August) 1946.

Covalt, Donald A.: Medical Rehabilitation for Paraplegia Veterans, Handicap, 1: 4 (September) 1947.

Deaver, George G.: Functional Education in Rehabilitation, Surgical Clinics of North America, April, 1945, pp. 374-381.

Metropolitan Life Insurance Company, Statistical Bulletin, Vol. 27, No. 3, March, 1946, pp. 3-5.

Metropolitan Life Insurance Company, Statistical Bulletin, Vol. 27, No. 11, November, 1946, pp. 7-8.

Metropolitan Life Insurance Company, Statistical Bulletin, Vol. 28, No. 7, July, 1947, pp. 5-7.

Knudson, A. B. C.: Activities of the Veterans Administration in Rehabilitation, Occupational Therapy and Rehabilitation, 25: 191 (October), 1946.

Knudson, A. B. C.: The Medical Rehabilitation Program of the Veterans Administration, Military Surgeon, 100: 323 (April), 1947.

Knudson, A. B. C.: Dynamic Aspects of Physical Medicine in the Veterans Administration, Archives Physical Medicine, 29: 29 (January), 1948.

Kovacs, Richard: Editor of 1946 Yearbook of Physical Medicine; Year Book Publishers, Chicago, Illinois, 399 pages.

Krusen, Frank H.: Physical Medicine, W. B. Saunders Company, Philadelphia, 1941, 846 pages.

Krusen, Frank H.: Physical Therapy in Relation to General Practice, Ohio State Medical Journal, 39: 530 (June), 1943.

Krusen, Frank H.: The Future of Physical Medicine, JAMA, 125: 1093 (August 19), 1944.

Piersol, George M.: The Value of Physical Therapy in Internal Medicine, JAMA, 117: 1835 (November 29), 1941.

Rusk, Howard A.: Rehabilitation, *New York Times*, Editorial, September 22, 1946.

Rusk, Howard A.: Rehabilitation, *New York Times*, Editorial, June 29, 1947.

Rusk, Howard A.: Rehabilitation and Early Ambulation, *Modern Medicine*, January 1, 1948.

Rusk, Howard A.: Rehabilitation in Operation, *Southern Medical Journal*, 41: 57 (January), 1948.

AGE AND THE ENDOCRINE GLANDS

C. E. HALL*

The increasing number of clichés appearing in the literature contribute little to an understanding of the processes to which they are applied. Such terms as "a man is as old as his arteries" or "a man is as old as his connective tissues" are becoming increasingly prevalent despite their obvious oversimplification. They do not clarify our insight into the processes involved in ageing, nor do they explain the physiology of the fundamental changes occurring in the various organ systems which are themselves held to be the cause of senescence. It is not surprising therefore, that the glands of internal secretion have failed to escape the stigma of responsibility for ageing and it has been said that "a man is as old as his endocrines." The evidence for and against this statement appears to be deserving of investigation. Such aphorisms if repeated often enough come to be accepted as fact despite the paucity of evidence adduced in their support.

THE THYROID GLAND

Hypothyroidism results in a profound reduction of tissue oxidation with concomitant reduction of growth, repair, resistance to infection and a tendency to fatty degeneration of muscle and other tissues. The anomalies which accompany myxedema and cretinism in man are too well known to require recapitulation. Perhaps the most interesting feature of prolonged thyroid hypofunction is the fact that while certain symptoms such as cutaneous edema, low basal metabolic rate and reduced cardiac output are reversible by adequate thyroid therapy, others such as the impairment of growth and mental development which occur in the prepubertal hypothyroid individual are not.

It is known that, in man, there is a gradual reduction in the basal metabolic rate of otherwise healthy individuals after the

*From the Carter Physiology Laboratory, The University of Texas Medical Branch, Galveston. Presented as part of the Seminar Series on the Process of Ageing, conducted at the Medical Branch, March, 1948.

age of 20–25. Lorand (1910) conceives this to be an indication of advancing hypothyroidism and cites the concomitant decrease in muscle tone, muscle efficiency, increased body weight, and dryness of the skin characteristic of both aged and myxedematous individuals in support of this contention. This hypothesis however, fails to explain or account for the fact that many aged individuals actually decline in weight to the point of emaciation, or for the gradual but significant ascending curve of intellectual processes which continues long after the alleged onset of hypothyroidism. It seems probable that there is a decline of thyroid function with advancing age, but unless this can be demonstrated to be below bodily requirements for thyroid hormone a state of thyroid hypoactivity cannot be said to exist. Marked thyroid hypertrophy associated with a raised basal metabolic rate occurs during pregnancy, indicating that the thyroid is able to respond to increased metabolic demands; since normal pregnancies are possible into the fifth decade of life, it seems unreasonable to assume a significant thyroid failure occurring after 25–30 years of age.

It seems to be established that the thyroid glands of individuals from 40–65 years of age are smaller, showing small follicles and lower epithelial cells, less colloid, sclerosed blood vessels and more connective tissue than is the case in younger people (Cooper 1925). Peculiarly, however, these facts have been variously interpreted as being indicative of hyper-and hypo-function. Proponents of either view have failed to explain the inconsistencies inherent in the assumptions, some of which are cited above.

The thyroid glands of mice undergo gradual and progressive sclerosis with increasing age which eventually culminates, in very old animals, in almost complete obliteration of normal structure. The acini become surrounded by bands of dense hyaline material which, presumably by interference with the nourishment of the epithelium, results in extensive destruction thereof. These changes are partially reversed by the administration of thyrotropic hormone (Loeb 1940). The hypertrophic and hyperplastic changes in the structure of the gland consequent to such treatment are accompanied by an increased amount of tissue fluid which induces a sort of rejuvena-

tion in the structure. A similar change in thyroid structure with age has been observed in the rat, but other animal species have been relatively neglected.

The Parathyroid Glands

These glands which are intimately concerned with calcium and phosphorus metabolism have been suspected of an etiologic role in the osseous changes which often accompany old age. Changes in the histologic structure of the gland with advancing age have been described. Cooper (1925) claims that the parathyroids of man are more vascularized in older individuals than in young. In mice Loeb (1940) has shown that in the parathyroids of older individuals, the cell strands are separated by thick bands of dense hyaline tissue. This sclerosis is characterized by its periarteritic rather than end-arteritic distribution. The sclerotic changes in both thyroid and parathyroids of mice show a great strain variation. They have been described as absent in CBA, rare in Buffalo, intermediate in A and D, while in C_3H and above all C57 almost every old mouse is thus affected. In aged men and women the bone calcium has been described as normal, increased or decreased in quantity, but there exists no clear-cut evidence that the parathyroid glands are responsible in any way for the deviations from the normal.

The Adrenal Glands

The adrenal glands have assumed a position of great importance of recent years and our knowledge of their role in physiologic and pathologic conditions, while by no stretch of the imagination complete, is extensive.

The general asthenia, disturbed gastrointestinal function, tendency to increased pigmentation and low basal metabolic rate are symptoms common to both adrenal cortical insufficiency and old age. It is not surprising, therefore, that a decline in adrenal cortical function has been postulated in old age and held responsible for much of the symptomatology of the ageing phenomenon. It should be remembered, however, that while hypotension always accompanies severe adrenal cortical insufficiency it is not a common accompaniment of old age, indeed

hypertension is more frequently encountered. Normal or even hyperplastic cortices have been described in aged individuals.

Recently Albright (1947) has described a condition occurring in older individuals characterized by osteoporosis in both sexes and by loss of axillary and pubic hair in females with concomitant decline in 17-ketosteroid output which is ascribed to a declining cortical function. The development of axillary and pubic hair in the female is thought to be controlled by those hormones elaborated by the adrenal cortex which also control nitrogen metabolism. Since the menarche and "adrenarche" are concurrent, axillary and pubic hair develops at puberty. The waning of adrenal cortical function with respect to the hormones concerned with nitrogen metabolism or "adrenopause" usually occurs somewhat later in life than the menopause. Osteoporosis developed at this time is due to a deficient deposition of bone matrix. There is no evidence of a decreased production of the adrenal cortical hormones concerned with carbohydrate metabolism, the 11-oxycorticoids, at any period of life. It is impossible at the present time to correlate changes in the mitochondria, siderophilia and other cytologic elements of the adrenal cortex alleged to occur in the aged with the "adrenopause," because our knowledge of the cells of the cortex concerned with the elaboration of the many hormones which it is known to produce is limited. Determination of the cholesterol and ascorbic acid content of adrenal cortices enable us to distinguish between a gland which is hyperactive and one which is normal since these substances are always decreased in the former condition, but is of little use in detecting quantitative shifts in hormone production by the adrenal cortex. The observations of Albright, however, seem to establish clearly that in man there tends to be a decline with age, in the production of the adrenal hormones controlling nitrogen metabolism while those concerned with carbohydrate metabolism are produced in undiminished quantity.

The adrenal cortices of mice (Loeb, 1940) show several cytologic alterations which have definite time curves. These typically consist of a downgrowth of spindle cell connective tissue from the capsule which may, in older mice, completely destroy parts of the cortex; a hyperemia and hemorrhage at

the cortico-medullary junction; and lastly a hyalinization of fasciculate cells with the formation of yellow vacuolar cells and fat-like tissue between the cortex and medulla. The first two of these alterations appear to be partly sex-controlled since they are more common and severe in females. The third change, encountered in both sexes shows a strong strain predilection.

There appears to be no convincing evidence of changes in either the structure or the function of the adrenal medulla with age. Various theories have been advanced from time to time postulating a slight hyperactivity of the adrenal medulla which, acting over a long period of time, leads to degenerative vascular lesions and generalized arteriosclerosis. These have been outstandingly deficient in factual proof and are now generally discounted.

The recent work of Vogt (1943), who has claimed that the perfusion of the adrenal glands with adrenalin solutions results in a several fold increase in the discharge of hormones from the adrenal cortex, invites speculation. The possibility of medullary hyperactivity inducing pituitary and adrenal cortical imbalance may offer further insight into such hitherto puzzling phenomena as Cushing's syndrome, adrenal cortical adenomata and allied disturbances which tend to be more prevalent in older individuals.

The Ovaries

Ageing of the human ovary in the reproduction sense, begins at the menarche when the loss of "endowed capital" in the form of ova begins (Hertig, 1944). Inasmuch as it has not been proved that ovogenesis is possible in the adult human female it appears that ova must become progressively less in number until they disappear from the ovary. Involution and atresia of the ovary have been widely studied in both man and experimental animals. Arai (1920) noted the gradual diminution in the number of ova in the rat ovary with advancing age. Curiously enough there was a greater decrease in number from birth to weaning age (35,000 to 10,000) than from weaning to puberty (from 10,000 to 5,000). A similar phenomenon is thought to occur in the human. This sequence of events has

been ascribed to inherent hereditary factors and to a differential blood supply, but these are purely hypothetical explanations.

Concurrent with the loss of ova at ovulation, and the atresia of numerous ova which do not reach a mature state and hence fail to ovulate, there is throughout life a gradual thinning of the cortex and an increased wrinkling of the ovarian surface. Connective tissue increases as corpora lutea are transformed into corpora albicantes and atretic follicles undergo fibrosis. Menopause in the female usually occurs between 20 and 60 years of age, in 65% occurring between 45 and 55. In general it may be said that there is cessation of follicular activity after 50 years of age, although menstruation in an individual of 73 years has been reported.

In mice the principal changes with advancing age are a decrease in the number of preserved follicles and an increase in interstitial elements; a decrease in the number of preserved or degenerated corpora lutea and an increasing hyalinization of the blood vessels in the hilus and medulla (Loeb, 1940). The corpora lutea of rats decline in number rapidly after 18–19 months of age, wheel cells make their appearance and cystic follicles first occur in 12-month old rats and increase with advancing age.

In women there is apparently a primary ovarian failure, since following normal menopause or menopause consequent to X-irradiation, disease or operative removal of the ovaries there appears in the blood increased quantities of follicle-stimulating hormone produced by the anterior lobe of the pituitary. Similarly the ovary is refractory to injected gonadotrophic hormones (Watson, Smith and Kurzrok, 1938). The reactivation of senile ovaries in mice by the implantation of anterior lobe tissue has been reported, indicating that in these animals the cessation of reproductive life in the female is at least partially due to waning hypophysial function.

The Testes

The male gonads consist of two types of tissue essential to their function. These are the germinal epithelium responsible for the production, development and maintenance of the germ cells; and the Leydig or interstitial cells, concerned with the

elaboration and secretion of the testicular hormones. Each of the components responds to a specific pituitary hormone, the former being under the influence of follicle stimulating hormone (F.S.H.) and the latter being controlled by the interstitial cell stimulating hormone (I.C.S.H.) which is apparently identical with the luteinizing hormone (L.H.) of the female.

With advancing age in the male there is increased pigment deposition in the cells of the efferent tubuli, in the smooth muscle of the prostate and seminal vesicles and in the Leydig cells. These are very abundant in men past 60. It has been stated that often in very old individuals the only cells which can be identified with certainty as Leydig cells are those which bear pigment (Engle, 1939). Evidence of declining 17-ketosteroid output with age has been obtained by Fraser *et al.* (1941) and by Salter, Cohen and Sappington (1946) but others have not noticed this age correlation except in men of the 7th and 8th decades of life (Venning and Kazmin, 1946). This probably represents a declining gonadal failure in males comparable to that which is known to occur in the female. In the male, however, instances of normal testicular function in aged individuals are far more common than in the female and waning gonadal function is not an invariable accompaniment of age in males.

In addition to these changes there occurs a thickening of the basement membrane which leads to hyaline changes in the seminiferous epithelium and surrounding tunica propria. These may be the result of impaired vascular supply, since they are not observed in all individuals. Indeed they may be quite marked in young individuals of 19–25 and completely absent in the extremely aged.

The Hypophysis

The multiplicity of hormones elaborated by the anterior lobe renders it possible to explain almost any or all of the features characteristic of old age on the basis of abnormalities in the function of this gland. The premature ageing of patients suffering from Simmonds' disease, which is due to a deficiency of anterior lobe hormones, is one of the most prominent features of the disease. Hyalinization of the anterior lobe has also been

reported in a case of progeria. Our present knowledge of the functions of the anterior lobe does not however, permit us to assess accurately the precise relationship between hypophysial activity and the process of ageing. Certain structural changes do apparently take place in the gland with advancing age, and shifts in hormone production, such as those consequent to menopause in the female, are known to occur.

Perhaps the most characteristic change within the pituitary with age is the invasion of the basophilic elements into, and increased pigmentation of, the posterior lobe. The significance of these changes has been speculated upon in some detail, but still remains obscure. In his series of 800 pituitary glands Simmonds (1914) found a slight decrease in weight with age. In a series of 107 pituitary glands Parsons (1936) observed that the invasion of basophilic cells into the posterior lobe roughly paralleled age in both males and females. Rasmussen (1936) has reported that there is a significant increase in chromophobes and a decrease in the number of acidophiles in both men and women above 50, and an increase in the number of basophiles in old women but not in old men. With this increase in chromophobic elements, which are presumably nonfunctional in an endocrine sense, there is also increased connective tissue formation.

In contrast to these observations, Severinghaus (1944) claims that both the acidophilic and basophilic cells of post-menopausal women show pronounced cytologic evidences of hyperactivity when compared with glands from younger women or older men. This is in agreement with the known fact that increased quantities of hypophysial gonadotrophic hormones appear in the urine of post-menopausal women. Still others have remarked upon the extreme anatomic and cytologic stability of the anterior lobe between the ages of 20–80 although there does appear to be a slight but progressive diminution of the blood supply of the usually vascular hypophysis after the age of 50–60.

A progressive diminution in the number of eosinophiles and basophiles with a concomitant increase in chromophobic elements with age has been reported in the rat (Wolfe, 1943) (Wolfe, Bryan and Wright, 1938). It seems to be generally

agreed that in old rats of both sexes there is generally histologic evidence of decreased secretory activity of the cells. However, for the most part these changes are well advanced while the rat is only 12 months old and in the prime of life.

Although it appears certain that changes in both structure and function of the anterior lobe do occur with age, it would be unwise to undertake an attempt at an accurate analysis of their role in the process of ageing. The obviously important part played by the anterior pituitary in growth and repair processes through secretion of the growth hormone, the evidence of age changes synchronous with the decreased production of this hormone after full somatic growth is attained, and the premature ageing of patients with Simmonds' disease all indicate the importance of this gland in ageing processes. Our knowledge does not permit of an accurate evaluation of the precise degree to which it is responsible for the atrophic and degenerative changes of age. Cytologic or other evidence of an altered structure or function of the posterior lobe of the pituitary gland with age, other than the invasion of basophilic cells from the anterior lobe already described, is lacking.

The Pancreas

Diabetes mellitus is one of the more confusing endocrinopathies. It is now recognized that the symptoms of the disease may be elicited experimentally by injections of thyroid hormone, adrenal cortical hormones of the 11-oxycorticoid series and anterior pituitary extracts. Clinical counterparts of these exist and thyroid, adrenal, pituitary and pancreatic diabetes are now recognized. It appears to be probable that even in pancreatic diabetes the other endocrines participate in the symtomatology and pathogenesis of the malady. The normal homeostatic mechanisms fail, and the continued formation of carbohydrates from proteins in the liver due to stimulation by the adrenal cortical hormones probably accounts, in part at least for the disturbances in carbohydrate metabolism consequent to a deficiency of insulin. Certain instances of islet-cell failure may be precipitated by undue strain imposed upon them by hyperactivity of the hypophysis or adrenal cortex and

consequent excess carbohydrate formation. This is supported by the experimental observations that repeated injections of anterior lobe extracts produce typical symptoms of diabetes in the dog and hydropic degeneration of the islets of Langerhans in the pancreas which is found to be deficient in insulin content (Best, Campbell and Haist, 1939) (Campbell and Best, 1938).

One of the most confusing aspects of the disease is the fact that in many diabetics coming to autopsy, the percentage has been variously estimated at 20% to 40%, examination following serial section of the gland fails to reveal any cytologic abnormality in the islet cells. Similarly marked lesions may be present in the glands of patients who have never evidenced diabetic symptoms. This serves to emphasize that frequently only the grossest cellular abnormalities are reflected in obvious lesions. Metabolically indisputable evidences of disturbed organ function are frequently unaccompanied by any demonstrable pathologic change in structure. It should also be borne in mind that the reserve capacity of many organ systems is such that a considerable proportion of cells may be destroyed without inducing evidences of impaired function.

The uncertainty of the relationships between detectable pathologic lesions of the pancreas and impaired carbohydrate metabolism render it hazardous to assess the effects of age on pancreatic incretory efficiency.

An extensive survey carried out by Joslyn and Dublin (1936) indicates that frank diabetes or definitely lowered sugar tolerance reach the peak of incidence during the 4th or 5th decade of life. From 60 on there occurs a marked decline. Actually the peak probably occurs earlier than this, since diagnosis takes time and the incipient stages are often confusing. The occurrence of diabetes in infants of one or two years of age, its absence in very old people and the marked decline in occurrence after 60 years of age argue that pancreatic insufficiency is not due to old age *per se*. Atrophic, sclerotic and hydropic changes have been described in the islets of Langerhans of aged individuals both diabetic and non-diabetic. The relationship which these changes bear to the phenomenon of old age is uncertain at best.

The Kidneys

No purpose would be served by an extensive review of the voluminous data which has accumulated in recent years regarding the endocrine nature of the kidney. The work of Tigerstedt and Bergmann (1898) of Goldblatt and his collaborators (1947) and of numerous others has established beyond doubt that, in addition to their purely exocrine function, the kidneys also elaborate and secrete into the circulating blood the enzyme renin which fulfills the requirements of a hormone. While the role which renin plays in the induction of experimental renal hypertension is well known and has been reviewed thoroughly elsewhere (Blalock, 1940; Goldblatt, 1947), recent observations indicate that in the chronic phase of hypertension induced by the Goldblatt method the elevated blood pressure is maintained by a neural rather than humoral mechanism (Ogden, 1947). Therefore the precise relationship which it bears to the pathogenesis of the various clinical forms of arterial hypertension, especially the so-called "essential hypertension" remains obscure. However, in view of the fact that there exists some evidence implicating the kidney in human essential hypertension (Goldblatt, 1947) and that about 23% of all deaths of persons over 50 years of age is attributed to hypertension or the degenerative vascular lesions which accompany it (Fahr, 1928) it seems pertinent to consider to what extent the passage of time is reflected in renal structure.

In the study of a large number of arteriosclerotic individuals it was found (Moritz and Oldt, 1937) that despite extensive arterio-or arteriolar sclerosis, such changes were consistently associated with hypertension only when they occurred in the kidney. Of 100 non-hypertensive individuals, one-third of them over 60 years of age, none showed severe arteriolar lesions while those of a mild grade were discovered in only 16. In a series of 100 hypertensives of comparable age, however, 97% showed arteriolar involvement, this being of severe grade in 47%. Thus it appears that if the renal arterioles become involved in the general vascular changes resulting from senescence, hypertension accompanies them. It is not entirely clear whether the arteriolar changes are antecedent or consequent

to the hypertension, but arteriolo- and arteriosclerosis are essentially diseases of old age. Unfortunately it is not possible (Fahr, 1925) to distinguish benign nephrosclerosis of vascular origin from simple senile atrophy, if indeed these are distinct and separate entities, and therefore impossible to differentiate between those changes which are due to old age *per se* and those which represent the end-result of small vascular disturbances.

Human kidneys grow relatively rapidly during the first twenty years of life, slowly from then until the peak of about 260 grams at the end of the third decade, and rapidly decline to about 180 grams at the age of 85 (Roessle and Roulet, 1932). This shrinkage is confined to the cortex. In the seventh decade of life the number of glomeruli is reduced by one-third to one-half that of early adult life (Moore, 1931). A similar condition has been described in the rat over its much shorter life span (Arataki, 1926) (Moore and Hellman, 1930). Similarly there is a gradual reduction of the number of glomeruli in the kidney of the daddy sculpin with time so that eventually the glomerular kidney becomes entirely aglomerular in very aged individuals (Grafflin, 1933).

Vascular changes occur with advancing age in the kidney as elsewhere in the body. Typical changes consist of a duplication of the elastic fibrils of the intima in the renal arteries. The terminal arterioles frequently show a thickening and hyalinization. Occasionally there may be an accompanying deposition of lipoid material in the vessel wall. These changes begin in infancy and increase in degree with advancing years (Oppenheimer, 1918). When such changes attain a severity which seriously impairs the nutrition of the tissues served by the vessel or vessels in question, these undergo degeneration and are eventually replaced by scar tissue. Thus, depending upon whether the large or medium sized arteries are chiefly affected and whether or not there has been extensive involvement of the smaller arteries and arterioles, the terminal picture varies. A relatively normal sized organ with scattered retracted scars is encountered if the first condition has obtained, while a general reduction in size accompanied by diffuse granular scarring is typical of the latter event. Obviously intergradations between these two extreme conditions may occur and therefore

the final pattern of the renal parenchyma is subject to great variation. Needless to say atrophy, degeneration and disruption of the tubular elements also accompany the vascular changes.

It is obvious then that certain changes in renal structure do occur with the passage of time. So great, however, is the safety margin of the kidney that in the past little alteration in the functional efficiency of the organ has been detected. Early investigations showed, however, that these changes are reflected in waning renal efficiency and that individuals among the aged have a higher level of inroxyl and urea in the blood and excrete phenolsulphonphthalein at a slower rate than those among the younger age group (Laroche, 1933). Recently Shock (1946) has carefully compared the glomerular and tubular efficiency of aged and young males, selected for the absence of symptoms or previous histories of cardiovascular-renal disease by the inulin and diodrast clearance techniques. This study reveals that aged men suffer a marked impairment of both functions, the decrease in tubular function being especially pronounced.

The lack of precise knowledge as to the cells responsible for the elaboration and secretion of renin renders futile any attempt to correlate the age changes in the renal parenchyma with prehypertensive changes, although the disturbance in intra-renal hemodynamics consequent to the development of severe arterio- and arteriolosclerosis undoubtedly favors such an occurrence.

Conclusions

Any evaluation of ageing as it applies to the human body must necessarily discriminate between chronologic age and physiologic age, which are quite different entities. Physiologic age is a composite phenomenon in which genetic influences and environmental forces, both internal and external, are involved and is the type of age with which we are primarily concerned. Obviously if the onset and development of the changes which contribute to the functional ageing of the various tissues and organs of the body could be delayed or arrested a longer period of life or chronologic age would result. Evidently the physiologic life span is not the same for all of the organ systems of the body.

The reproductive capacity of the female gonads is lost long before signs of advanced age manifests themselves on the body. As a consequence thereof the accessory structures such as the vagina, mammae and uterus undergo atrophic changes. Despite this however, the nervous, digestive, respiratory and other systems of the body continue to function in their accustomed manner without evidences of severe impairment.

Our knowledge of the influences of the endocrine glands upon each other and upon the body as a whole is by no means complete. On the basis of what is at present known of their functions, however, it is safe to state that neither any single endocrine gland, nor any combination of them, may be held solely responsible for the physical ravages characteristic of old age, although they undoubtedly play a contributory role. In general there is a tendency for evidences of hypofunction to be manifest in endocrine glands with advancing years beyond puberty and a concomitant increase in fibrous tissue within them, but these are features common to many other tissues and organs and it does not seem warranted to implicate the glands of internal secretion either singly or collectively as the etiologic agent in old age. It seems likely that the endocrines are themselves the victims of decreased blood supply incident to the generalized vascular sclerosis so characteristic of the ageing process, and their consequent decreased efficiency plays a contributory part in the atrophic and degenerative changes which ensue. The decline in endocrine activity may be a response to slowing bodily functions; once a marked involution occurs, it may serve to inhibit or accentuate retrogressive changes in other organs.

BIBLIOGRAPHY

Albright, F.: Osteoporosis, *Ann. Int. Med.*, 27:861, 1947.

Arai, H.: On the Postnatal Development of the Ovary (albino rat) with Especial Reference to the Number of Ova, *Am. J. Anat.*, 27:405, 1920.

Arataki, M.: On the Postnatal Growth of the Kidney with Special Reference to the Number and Size of the Glomeruli (albino rat), *Am. J. Anat.*, 36:390, 1926.

Best, C. H., Campbell, J., and Haist, R. E.: The Effect of Anterior Pituitary Extracts on the Insulin Content of the Pancreas, *J. Physiol.*, 97:200, 1939.

Blalock, A.: Experimental Hypertension, *Physiol. Rev.*, 20:159, 1940.

Campbell, J., and Best, C. H.: Production of Diabetes in Dogs by Anterior Pituitary Extract, *Lancet*, 234:1444, 1938.

Cooper, E. R. A.: *The Histology of the More Important Endocrine Organs at Various Ages*, Oxford Press, 1925.

Engle, E. T.: *Cowdry's Problems of Ageing*, Williams and Wilkins Co., Baltimore, 1939.

Fahr, G.: Hypertension Heart, *Am. J. Med. Sci.*, 175: 453, 1928.

Fahr, Th.: *Handbuch der Speziellen Pathologischen Anatomie und Histologie*, Berlin, 6: 374, 1925.

Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H., and Reifenstein, E. C.: Colorimetric Assay of 17-ketosteroids in Urine, *J. Clin. Endocrinol.*, 1: 234, 1941.

Goldblatt, H.: The Renal Origin of Hypertension, *Physiol. Rev.*, 27:120, 1947.

Grafflin, A. L.: Glomerular Degeneration in the Kidney of the Daddy Sculpin (Myxocephalus Scorpius), *Anat. Rec.*, 57:59, 1933.

Hertig, A. T.: The Ageing Ovary—a Preliminary Note, *J. Clin. Endocrinol.*, 4: 581, 1944.

Joslyn, E. P., and Dublin, L. I.: Studies in Diabetes Mellitus, *Am. J. Med. Sci.*, 191: 759, 1936.

Laroche, G., Schulman, E. et Desbardes: L'indoxylemie chez les Vieillards, Compte rend. *Soc. de Biol.*, 112: 290, 1933.

Loeb, L.: *Hormones and the Process of Ageing*, Harvey Lect., 36:228, 1940.

Lorand, A.: *Old Age Deferred*, Phila., 1940.

Moore, R. A.: The Total Number of Glomeruli in the Normal Human Kidney, *Anat. Rec.*, 48:153, 1931.

Moore, R. A., and Hellman, L. M.: The Effect of Unilateral Nephrectomy on the Senile Atrophy of the Kidney in the White Rat, *J. Exper. Med.*, 51:51, 1930.

Moritz, A. R. and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, *Am. J. Path.*, 13:679, 1937.

Ogden, E.: The Extra Renal Sequel to Experimental Renal Hypertension, *Bull. N.Y. Acad. Med.*, 23:643, 1947.

Oppenheimer, F.: Uber den Histologischen Bau der Arterien in der Waschsenden und Alternden Niere, *Franf. Ztschr. f. Path.*, 21:57, 1948.

Parsons, R. J.: *Medical Papers Dedicated to H. A. Christian*, Waverly Press, Baltimore, 1936, p. 366.

Rasmussen, A. T.: The Pituitary Gland, *Proc. Assoc. Res. in Nerv. and Ment. Dis.*, 17:118, 1936.

Roessle, R. et Roulet, F.: *Mass und Zahl in der Pathologie*, J. Springer, Berlin und Wein, 1932, p. 144.

Salter, W. F., Cohen, R. L., and Sappington, T. S.: 17-ketosteroids in Metabolism. Partition of Gonadal and Adrenocortical Hormonal Derivatives of Normal, Endocrine and Cancerous Patients, *J. Clin. Endocrinol.*, 6:52, 1946.

Severinghaus, A. E.: Cytology of the Anterior Pituitary Gland of the Post-Menopausal Woman, *J. Clin. Endocrinol.*, 4: 583, 1944.

Shock, N. W.: Kidney Function Tests in Aged Males, *Geriatrics*, 1:232, 1946.

Simmonds, M.: Uber Embolische Prozesse in der Hypophysis, *Virchow's Arch.*, 217:226, 1914.

Tigerstedt, R., und Bergmann, P. G.: Niere und Kreislauf, Skand, *Arch. f. Physiol.*, 8:223, 1898.

Venning, E. H., and Kazmin, V.: Excretion of Urinary Corticoids and 17-ketosteroids in the Normal Individual, *Endocrinal.*, 39:131, 1946.

Vogt, M.: The Output of Cortical Hormone by the Mammalian Suprarenal, *J. Physiol*, 102:341, 1943.

Watson, B. P., Smith, P. E., and Kurzrok, R.: The Relation of the Pituitary Gland to the Menopause, *Am. J. Ob. and Gyn.*, 36: 562, 1938.

Wolfe, J. M.: The Effects of Advancing Age on the Structure of the Anterior Hypophyses and Ovaries of Female Rats, *Am. J. Anat.*, 72: 361, 1943.

Wolft, J. M., Bryon, W. R., and Wright, A. W.: Histologic Observations on the Anterior Pituitaries of Old Rats with Particular Reference to the Spontaneous Appearance of Pituitary Adenomata, *Am. J. Cancer*, 34: 352, 1938.

MEDICAL ASPECTS OF THE TEXAS CITY DISASTER WITH SPECIAL REFERENCE TO THE EFFECTS OF AIR BLAST

DAVID MINARD, JOHN H. KILLOUGH AND BERNARD ZIMMERMAN*

On 16 and 17 April, 1947, within a period of sixteen hours, two ships exploded in the harbor of Texas City, Texas. The first was the Grandcamp, a French ship carrying 2300 tons of ammonium nitrate fertilizer. Fire was discovered in her number four hold at approximately 0800, 16 April, and at 0912 the ship exploded. During the afternoon, fire was discovered aboard a nearby ship, the High Flyer, and at 0110, 17 April, this ship loaded with 961 tons of ammonium nitrate also exploded. These explosions and the subsequent fires which took place resulted in a death toll of approximately 500 and injuries to 2000 or more persons, 824 of whom required hospitalization. Property damage was estimated at fifty million dollars. The physical aspects of the blasts have been described extensively by Dick, Lubelsky and Russel (1).

The medical organization, set up to cope with the emergency and definitive treatment of nearly three thousand injured survivors, was prompt and effective. First aid treatment was administered in emergency stations in Texas City, and by first aid squads at the site of the disaster. After preliminary examination and treatment, the serious casualties were further evacuated to hospitals in Galveston and Houston. The Galveston hospitals admitted a total of 710 patients; the Houston hospitals, 114. John Sealy Hospital, the teaching hospital for the Medical Branch of The University of Texas in Galveston, received the largest number of survivors.

Shock and traumatic injuries were treated following principles established during the recent war. Blood and plasma were extensively employed and debridement of wounds without primary closure was practiced in most instances.

---

*From the Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland. Submitted March 23, 1948.

It seemed worth-while to investigate the nature and extent of injuries following this explosion, for although it involved a much greater charge of explosive material than is contained in conventional high-explosive shells, its magnitude approached that of the explosive weapons that may become common in future warfare. In this regard, the over-all distribution of injuries, the incidence and type of burns, and the incidence of so-called "atmospheric blast injuries" seemed important. In 1946, Corey reviewed the literature on blast injury and discussed the experiments the Navy had carried out (2). He came to the conclusion that "airblast" *per se* as opposed to "immersion blast" was not a serious military hazard. His conclusions were also based on the findings in the "Norfolk blast" of September, 1943, which resulted from the accidental detonation of several Torpex depth charges. No blast injuries even of eardrums were seen in 55 patients studied following this explosion. Nevertheless numerous injuries and many fatalities have been described as a result of primary air blast effect (3,4,5), and with the development of explosives of far greater violence, they may well become much more significant.

The mechanism of injury in atmospheric blast was first investigated by Hooker (6) and studied in detail by Zuckermann and his associates (7) at the time of the large-scale bombing raids over England.

The most generally accepted picture of the pathogenesis of air blast injury is as follows:

a. Although an explosive wave consists of both positive and negative pressure phases, trauma to living objects occurs only during the positive phase since the force of the negative component, which can never exceed one atmosphere, is inadequate to cause tissue damage.

b. A compressive wave is transmitted through tissue without harmful effect until it reaches the boundary of a medium of different density, *e.g.*, lung or air-filled intestine. At such an interface, as a result of different accelerative responses of the media, separation and destruction of tissue occurs.

c. Damage to pulmonary tissue occurs not by transmission of a pressure wave through the respiratory passages, as was

once believed, but by direct impingement on the chest wall from which the wave is carried to the lung.

In addition to these concepts, the work of Benzinger should be mentioned with regard to the causation of sudden death consequent to experimental atmospheric blast (8,9,10). He showed that air emboli in pulmonary veins were introduced by exposure of dogs to air blast and that these emboli caused death from coronary or cerebral occlusion.

Findings

Fatalities. Of the total 484 known dead, 381 were identified and 103 remained unidentified as of 15 May, 1947. Between 100 and 150 were still missing on that date.

The urgency of the medical situation and the lack of identification of the dead precluded the performance of necropsies on those killed by the blasts; hence information as to the cause of death in the grossly uninjured dead could not be obtained.

Approximately 5 per cent of the bodies seen in the morgue exhibited no evidence of external injuries. These may have sustained fatal blast effects or may have succumbed to asphyxia or drowning.

It was estimated, however, by Dr. Schofield, the pathologist at The University of Texas, that approximately 30 per cent of the dead were charred. Our own observations support this estimate. These casualties are believed to be victims who were either killed outright by the blast or who were so injured or trapped as to be consumed by the fires succeeding the blast. Flash burns were not observed either among the dead or among the survivors.

Survivors. The findings presented here are based on a survey of seven hospitals in Galveston and Houston. They are derived from our own clinical examination or the review of the hospital records of 344 patients who survived the initial blasts on 16 and 17 April. Almost all of these patients had multiple injuries. Table 1 presents a summary of the predominant injuries sustained by the group under survey. In this table, each patient is classified as to his most serious injury.

Our interest at Texas City concerned two general classes of injury, burns and blast injuries. In spite of the extensive fires

following the two main blasts, the incidence of burns requiring hospitalization was remarkably low. Of the 344 patients included in this survey only three had burns. On the basis of history and physical findings, two of these were classified as chemical burns sustained in the Monsanta plants. The third burn case suffered a compound fracture of the right femur and while attempting to remove the debris which pinned him down, he sustained first and second degree burns to his back and left arm from a nearby fire. He managed to escape, but others, less fortunate, were so injured or trapped as to preclude escape and these victims were literally charred.

TABLE I

Predominant injuries in 344 patients

Injury	Per cent
Simple fracture	23.8
Lacerations	23.8
Skull	22.9
Chest	9.0
Compound fracture	5.8
Eye	5.2
Traumatic amputation	4.1
Internal abdominal	2.2
Burns	0.8
Gas gangrene complication	0.6
Major vessel or nerve	0.6
Spinal cord	0.6
Abortion	0.6

Blast injuries. Blast injuries are designated as those injuries to the tympanic membrane, chest, and abdomen resulting from pressure alterations *per se.* The presence of pre-existing disease, as well as injury from flying objects, and from being thrown against obstacles, was considered in each case. Only in the absence of such factors could pure blast effect be considered as the primary casual agent.

Ear injury. Seventy-nine patients were investigated with regard to the presence or absence of hemorrhagic or serious discharge from the ears. Of these, 31 patients (or 39 per cent of the total) revealed this evidence of damage to the tympanic membrane of one or both ears. This group of 31 patients was

questioned with respect to (a) distance from the blast, and (b) whether indoors or outdoors at the time.

The results of this injury are given in Figures 1 and 2. It is apparent from Figure 1 that there is a close correlation between the percentage of patients sustaining ear injury and the proximity to the blast. Figure 2 illustrates the protection provided by enclosures to blast injury of the ear.

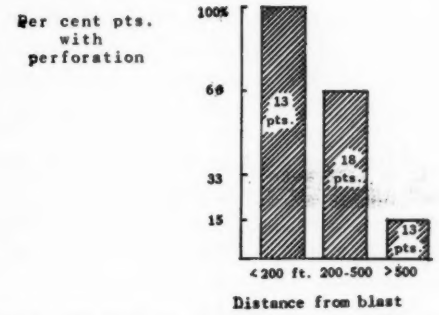


Figure 1.- The relationship of ear drum perforation to distance from the blast.

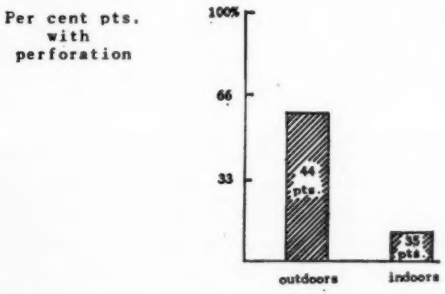


Figure 2.- The relationship of ear drum perforations to mechanical protection.

Pulmonary injury. Seven of the 344 patients exhibited symptoms and clinical findings which could be attributed to primary blast effects on the lungs.

Considering this group as a whole, certain symptoms and signs seem to be characteristic of this type of injury. As determined from the history, these included a sensation of

constriction in the chest at the time of the blast, followed by dyspnea, and deep-seated dull pain on inspiration. The dyspnea lasted up to 24 hours, and the pain persisted from one to five days.

Clinical examination of the chest revealed rhonchi, decreased breath sounds, broncho-vesicular breathing, and moist râles. Temperature elevation from 100° F. to 102° F. for two or more days after the blast was typical. All patients coughed frequently and brought up moderate quantities of muco-purulent sputum at some time during the period of hospitalization. Three of the patients coughed up small quantities of blood immediately after the blast and continued to do so after hospital admission.

Radiologic findings varied. Some revealed increased densities of a lobular character; others showed fan-like linear projections from the hilar regions, interpreted as interstitial hemorrhages. In others, plate atelectasis was seen. Lobular infiltrations and atelectases were limited to the lower lung fields.

These symptoms, signs, and radiologic findings had cleared within eight days in five of the patients. In one of the two remaining patients moist râles at the left lung base persisted through the eight-day period of our observations, and in the remaining patient a diagnosis of pleural fluid at the left base was established by X-ray at the time of our survey was terminated.

Abdominal injury. In none of the 2.2 per cent of patients who presented abdominal complaints could contusion from external causes be definitely eliminated; therefore abdominal injury will be considered in connection with the findings at laparotomy in one patient and the findings at autopsy in four cases who died after hospital admission.

The exploratory laparotomy was performed on the basis of a diagnosis of perforating wound of the abdomen. No perforation of a viscus was found but there were numerous ecchymoses in the greater omentum and mesentery.

Three of the four autopsies demonstrated similar lesions, the principal finding being retro-peritoneal ecchymoses. The fourth case at autopsy exhibited massive hemorrhage into the coro-

nary ligament of the liver, and subserous hemorrhage throughout the terminal 30 inches of the ileum.

All four cases at autopsy revealed extensive pulmonary damage characterized by subpleural ecchymoses and interstitial hemorrhage. Blood in the bronchi and alveoli was not apparent on gross examination. Death was attributed to intra-abdominal hemorrhage in two of these four cases and to skull fracture and brain damage in the other two.

Discussion

The absence of flash burns among those sustaining fatal injuries and among the survivors of the blast deserves comment. In all probability the explanation must be sought in the conditions under which the blast occurred. The ammonium nitrate was stowed in holds below the water line in ships tied to piers. These circumstances would tend to have a directional effect on both the air blast and the associated thermal wave. If this conception is correct the bystanders on the pier failed to sustain flash burns because the heat wave was deflected over their heads. Those in buildings above ground level would have been protected by the building walls. This reasoning might also be advanced to explain the otherwise miraculous escape from destruction by air blast of some individuals standing unprotected on the pier within one hundred feet of the ship.

It is most interesting, however, that despite the absence of flash burns, evidence of blast injury was seen. Thus the circumstances which offered protection from heat failed to prevent exposure to the latter type of injury. The history and physical and radiographic findings in the seven cases with pulmonary symptoms were very similar to those which have been described in similar cases by Palma and Enright (11), King and Curtis (12), O'Reilly and Gloyne (13) and others.

The high incidence of eardrum perforation also testifies to the magnitude of the pressure to which the survivors were subjected. The minimum force required to rupture the human tympanum has been variously estimated between 7 and 15 pounds per square inch. The protection that was afforded by buildings is in accord with the findings that have been made

experimentally with both physical measurements and animal studies.

With Benzinger's work in mind, the authors looked for evidence of arterial air embolism. Though occasional instances were observed of neurological findings such as transitory diplopia, inequality of pupils, or paresis of an extremity, the possibility of mechanical injury in these cases could never be completely ruled out.

Mention should be made of gas gangrene as a complication of wounds sustained in the Texas City blast. Great concern regarding this complication was felt by the physicians attending the victims for the first 72 hours after the disaster. The cause for this concern was the appearance of subcutaneous crepitus together with positive cultures for gas forming anerobes from wounds in some cases. However, in relatively few patients did frank gas gangrene develop. In the majority of cases, the infection was limited to the subcutaneous tissues and responded well to simple incision and to therapy with antibiotics and sulfonamides. The superficial anerobic infection was designated as anerobic cellulitis as opposed to gas gangrene which was of much lower incidence and required radical surgical treatment.

Summary

1. A survey was made of 344 survivors of the Texas City disaster which occurred 16 and 17 April, 1947.

2. Simple fractures, lacerations, and skull damage were the three most frequent types of injuries. Noteworthy was the rarity of burns among survivors. Among the dead, extensive burns with charring, were relatively common. Flash burns were noted neither in survivors nor in those killed by the blast.

3. Eardrum rupture was present in approximately 30 per cent of hospitalized patients. There was a relationship between the distance from the blast and the protection by enclosures to the incidence of ear injury.

4. Pure blast injury to the lungs and abdominal viscera was obscured in most cases by other types of injury. However, it is thought that such primary blast effects have been demonstrated in a small group of patients.

5. No autopsies were performed on victims killed outright by the blast. The gross pathological findings in four victims dying after hospital admission indicated primary blast injury to thoracic and abdominal viscera.

ACKNOWLEDGMENTS

The authors desire to express their appreciation to Drs. B. I. Burns, C. D. Leake, G. W. N. Eggers, E. J. Poth, R. M. Moore, N. D. Schofield, J. M. Thiel and M. Schneider of The University of Texas Medical School, and to Dr. W. V. Nesbitt of the U. S. Marine Hospital, Galveston, Texas, for their co-operation and generosity in making clinical material available for this study.

REFERENCES

1. Dick, F. F., Lubelsky, B. L., and Russel, C. R.: "Texas City Disaster —observations of fire and blast damage," Memorandum for Chief of Bureau of Ordnance, dated 2 June 1947.
2. Corey, E. L.: Medical aspects of blast, U.S. Nav. M. Bull., *46*:623, 1946.
3. Cohen, H., and Biskind, G. R.: Pathological aspects of atmospheric blast injuries in man, Arch. Path., *42*:12, 1946.
4. Fink, H.: Intestinal perforation resulting from atmospheric blast, U.S. Nav. M. Bull., *47*:884, 1947.
5. Hadfield, G., *et al.*: Blast from high explosives—Preliminary report on ten cases, Lancet, *2*:478, 1940.
6. Hooker, D. R.: Physiological effects of air concussion, Am. J. Physiol., *67*:219, 1924.
7. Zuckerman, S.: Experimental study of blast injury to lungs, Lancet, *2*:219, 1940.
8. Benzinger, T. H.: Detonationstod durch arterielle Luftembolie, Schrifften der deutschen Akademie der Luftfahrtforschung, 8:47, 1944.
9. Benzinger, T. H., and Rössle, R.: Luftembolie durch Luftstosswerkung auf die Lungen, Jahrbuch der deutschen Akademie der Luftfahrtforschung, p. 358, 1942-1943.
10. Benzinger, T. H.: In preparation in Aeromedical Survey—published by Air University (Randolph Field, Texas), Chapter on "Detonation Death."
11. Palma, J., and Enright, W. M.: Blast injury (concussion) of lungs, U.S. Nav. M. Bull., *40*:963, 1942.
12. King, J. D., and Curtis, G. M.: Lung injury due to the detonation of high explosive, Surg. Gynec. and Obst., *74*:53, 1942.
13. O'Reilly, J. N., and Gloyne, S. R.: Blast injury of lungs, Lancet, *2*:423, 1941.

DETERMINATION OF CODEHYDROGENASE I (COZYMASE) IN TUMOR TISSUES

A. Fisher and F. Schlenk*

Determination of Codehydrogenase I in Tumor Tissues

Warburg's studies on the metabolism of malignant tissues (18) have stimulated many investigations into the abnormal glycolytic pattern present in neoplasms (2). One theory suggests that uncontrolled growth may result from a deficiency of respiratory enzymes as compared with the energy-depleting enzymes present, such as those which hydrolyze phosphate esters (8). The discovery that neoplasms are deficient in cytochrome C (10), succinic acid dehydrogenase, and cytochrome oxidase supports such a conception. It seemed desirable, therefore, to extend the search to other biocatalsts involved in glycolysis and respiration. Since reports on the concentration of codehydrogenase I (cozymase; diphosphopyridine nucleotide) are particularly meager, we have studied its concentration in a variety of tumor tissues.

Both the oxidized forms (Co) and the reduced form (CoH_2; dihydro-) of the nicotinamide coenzymes occur in tissues. They exert their hydrogen-shifting activity by a continuous alternation between these forms (13). Since metabolism is an uninterrupted feature of living tissue, it is not surprising that upon extraction part of the coenzyme will be found in the reduced state. The two forms are differentiated by their stabilities in acid and alkali (12). Oxidized coenzyme is relatively stable in diluted acid, while dihydro-coenzyme is destroyed immediately. Conversely, oxidized coenzyme is destroyed rapidly in alkaline medium while dihydro-coenzyme is stable. The two forms can be determined separately by extracting tissue samples with 0.1 N HCl and 0.1 N NaOH respectively. Since the two forms alternate continually (13), the fermentation system is activated by either.

---

*From The University of Texas, Medical Branch, Galveston, and the M. D. Anderson Hospital for Cancer Research, Houston. Received for publication, April 6, 1948.

It has been shown that some tumor tissues show irregularities in the ratio: oxidized/reduced coenzyme (3). For example, Jensen rat sarcoma was found to have a concentration of dihydro-coenzyme which was 3 to 10 times higher than that of cozymase, while all other tissues have a higher concentration of cozymase (4). In the present study we tested other tumor tissues for this anomaly and for the total concentration of codehydrogenase.

Experimental Part

Fermentation Test: Of the various methods for determination of codehydrogenase I, the fermentation test appears to be the most suitable for the evaluation of tissue extracts. Its advantages have been summarized recently (16). The principle of the technique is the measurement of the fermentation rate of glucose with inactive yeast. The coenzyme is removed from the yeast by a washing process. Reactivation of the yeast by tissue extracts, resulting from their coenzyme content, is compared with a reference standard.

Reference Standard: The first prerequisite for the determination of the coenzymes is a reliable reference standard. Although it would be ideal to use an absolutely pure preparation, it is satisfactory in most instances to use a well-defined product of less than 100% purity, if corrections are made for the inert material. Cozymase preparations, even in the dry state, deteriorate noticeably within a few months and to a marked degree within a year. We evaluated our standard preparations by catalytic micro-hydrogenation (16), and by ultra-violet spectrophotometry of the dihydro derivative obtained by hydrosulfite reduction (11). We consider these two methods to be the most reliable for establishing the purity of the coenzyme preparation. Small amounts of the standard are dissolved in enough water to give a suitable concentration (15 to 25 gamma per ml.). These solutions are not very stable, even if kept in a refrigerator, and gradually lose activity (about 25% in a week). It is advisable to prepare a fresh standard solution every second day.

Accuracy of the Method: The accuracy of the apozymase fermentation test is $\pm$ 5% for purified coenzyme preparations

and ± 10% for tissue extracts. Duplicate or triplicate determinations were performed in all our experiments. The details of the procedure have been outlined earlier (16). In the present investigation we were interested in determining if any constituents of crude tissue extracts enhance or inhibit the fermentation test. P. S. Krishnan has reported that adenosine triphosphate exerts an accelerating effect on the fermentation rate of dried and washed yeast (7). This is contrary to our earlier experiences (15) and we believe that the discrepancy is due to a difference in the brand of yeast. We have reexamined this question with the yeast used in this series of experiments (brewer's yeast, generously supplied by Anheuser-Busch, Inc., St. Louis). Table I shows that adenosine mono-

TABLE I

Effect of Adenosine monophosphate (AMP) and Adenosine triphosphate (ATP) on the Fermentation Rate of the Apozymase System

Exp. No.	Fermentation Mixture	Rate of CO_2 Evolution: cu.mm. per 30 min.	
		With AMP	Without AMP
1	Apozymase	29	33
	Apozymase + Cozymase	156	145
		With ATP	Without ATP
2	Apozymase	82	88
	Apozymase + Cozymase	366	355

Warburg technique, composition of samples as given earlier (16). Two different apozymase preparations were used in Exp. 1 and 2. Concentration of activators per flask:

Cozymase: 25 μgm.

Adenosine monophosphate (AMP): 300 μgm.

Adenosine triphosphate (ATP): 300μgm., calculated as free acid.

phosphate (AMP) and adenosine triphosphate (ATP), even if added in a concentration ten times that of the cozymase, do not change the fermentation rate beyond the limits of experimental error. The concentration of adenylic acid and

adenosine triphosphate in tumors is far below this level (5). This also holds for the concentration of magnesium ion, which is low in the tumor extracts compared with the large excess added to the fermentation mixture. Manganese ion exerts a marked stimulation on the fermentation rate of magnesium-deficient apozymase, but not in the presence of the excess magnesium ion provided in our fermentation mixture. Besides, the manganese concentration in tumor tissues is low (17). This consideration also holds for phosphate ion, hexose phosphate, and glucose which are added to the fermentation mixture in comparatively large amounts. The concentration of salt resulting from neutralization of acid or alkaline tissue extracts does not alter the fermentation rate appreciably.

Optimum Conditions for the Extraction of Codehydrogenase I from Tissues: Previous experience has shown that the extraction procedure is the most serious source of error in cozymase determinations (14). The pitfalls may consist of: losses during storage or handling of the tissue prior to extraction; faulty technique in the extraction; storage and treatment of the extracts prior to testing. In order to elaborate the optimum conditions, the experiments compiled in Table II were carried out. Rat liver was used in many instances since it shows a particularly high cozymase content. Thus, any inadequacy in extraction becomes much more conspicuous than if tumor tissues were used. All values for tissue coenzyme concentrations given in this paper pertain to the fresh weight. The following conclusions were drawn from these experiments:

Tissues should not be stored in the frozen state because the codehydrogenase is not stabilized and disappears in a few hours (Exp. 1a–1e). Another disadvantage of frozen tissue is the excessive cooling it causes when added to the extraction fluid. Since the enzymes which destroy cozymase in tissues after death are inactivated by heat, and the quantitative extraction of cozymase depends upon the immediate destruction of these enzymes, the delay caused by the frozen tissue may introduce a severe error. The extracts, however, can be kept for some time at a low temperature without loss of activating power (Exp. 2a–2c). The destruction of cozymase by these autolytic enzymes occurs very slowly in whole tissue (6), but it is very

marked when the cell structure is impaired by homogenization (Exp. 3a and 3b). For quantitative extraction it is not sufficient to immerse the tissue briefly in boiling water and to homogenize afterwards. The debris must be heated for a few minutes for the extraction to be complete (Exp. 4a–4c). The results concerning the ratio: oxidized/reduced coenzyme will also depend on the extraction method. Since dihydrocozymase is oxidized by oxygen at elevated temperatures, it is impossible to extract both forms with water, later destroying either the oxidized or reduced form with alkali or acid. Experiments 5b and 5c in

TABLE II

Variation of the Extraction Technique for Codehydrogenase Determination.

Exp. No.	Experimental Conditions	Coenzyme found, μgm/gm. tissue.
1a	Rat sarcoma (AH), extracted and homogenized without delay at 100° for 3 minutes	74
1b	Same as 1a, but kept in frozen state prior to extraction for 1 hour	66
	for 5 hours	53
	for 24 hours	21
1c	Rat liver, extracted immediately	635
1d	Same liver, stored in crushed ice for 1 hour prior to extraction	602
1e	Same as 1d, but stored for 2 hours	402
2a	Rat liver extract, used for fermentation immediately	576
2b	Same extract, tested after 24 hours storage at 0°	568
2c	Same extract, tested after 5 days storage at 0°	518
3a	Rat liver, homogenized hot, kept at 100° for 3 minutes	587
3b	Same liver, homogenized at room temperature. After 15 minutes storage at 20°, extracted for 3 minutes at 100°	40
4a	Rat liver, kept in boiling water for 30 seconds, then homogenized	292
4b	Same as 4a, but kept in boiling water bath for 3 minutes, including homogenizing procedure	515
4c	Same; extraction time including homogenizing at 100° was:	
	5 minutes	491
	7 minutes	474
	9 minutes	412
5a	Rat liver, extracted with water at 100° for 3 minutes ($Co + CoH_2$)	346
5b	Same, extracted with boiling water, exposed afterwards to acid for destruction of reduced coenzyme ... (Co)	224
5c	Same as above, after extraction exposed to alkali ... (CoH_2)	63
5d	Extraction with 0.1 N HCl at 100° ... (Co)	180
5e	Extraction with 0.1 N NaOH at 100° ... (CoH_2)	136

Table II show that this method yields a ratio: Co/CoH_2 = 3.5/1, while direct extraction with alkali and acid (Exp. d and e) yields a ratio: 1.3/1. The final tissue extracts should be adjusted to pH 6.0 to 6.5, which is the optimum pH for activity in the fermentation test. The following outline of extraction is based on the experimental results given above.

Directions for Preparation of Tissue Extracts for Cozymase Determinations: If immediate extraction is impossible, the tissue should be kept in crushed ice. The homogenizing apparatus of Potter and Elvehjem (9) is used for grinding the tissue. The tissue (0.2–0.5 gm.) is weighed rapidly and introduced into 3.0 ml. of water in a homogenizing tube which has been previously placed in a boiling water bath. After heating for 30 seconds, the mixture is homogenized thoroughly, reheated in the water bath, and finally cooled in ice. The entire operation, from immersion to cooling, should not take more than 3 minutes. The pH is adjusted to 6.0–6.5, the volume of the solution is recorded, and the cell debris is then centrifuged off. Since some water is used to rinse the homogenizer, the final volume is usually around 10 ml.

To determine the oxidized and reduced forms of cozymase separately, acid and alkaline extractions are done in the same fashion as the water extraction. 3.0 ml. of 0.1 N HCl or 0.1 N NaOH are used respectively instead of water. After the pH is adjusted to 6.0–6.5, the final concentration of NaCl from external sources is around 0.03 m. One ml. of this solution does not significantly increase the salt concentration of the fermentation mixture (3.0 ml.). An equivalent amount of NaCl is added to the standard experiments with reference cozymase.

Cozymase Determinations in Tumor Tissue: Table III shows the results of cozymase determinations in some tumor tissues. Eight rat sarcomas, type AH, in various stages of development showed a coenzyme content which was low compared with other rat tissues (4). The ratio: oxidized/reduced coenzyme was about the same as found earlier in other rat tissues (averaging 1.7:1). This is in contrast to results obtained with Jensen rat sarcomas (3). Low values were also obtained with methylcholanthrene-induced rat tumors (Table III, Exp. 9 and 10) and mouse breast carcinoma (Exp. 11 and 12). The metabolic

features of tumor tissues have sometimes been compared with embryonic tissue and the low cozymase content of rat embryo is in line with this resemblance (1). It appears from the data presented here that there is a deficiency in codehydrogenase in animal tumors. The accumulation of reduced cozymase observed in Jensen rat sarcoma (3) is not a general characteristic of tumors. It is planned to extend these studies to human tumors.

TABLE III

Determination of Cozymase (Co) and Dihydro-cozymase (CoH_2) in Tumor Tissues.

Exp. No.	Tumor Tissue	Extraction with: HCl (Co)	NaOH (CoH_2)	H_2O (Co + CoH_2)
1	Rat Sarcoma AH	49	50	98
2	Same	67	91	180
3	Same	105	41	167
4	Same	113	29	157
5	Same	116	42	.....
6	Same	63	41	.....
7	Same	76	53	145
8	Same	165	84	240
9	Rat tumor (methylcholanthrene)	9	36	49
10	Same	31	21	45
11	Mouse breast carcinoma (C_3H)	75	42	124
12	Same	123	57	189
13	Rat fetus (16 days)	41	25	61
14	Rat fetus (shortly before parturition)	31	25	56

The authors are indebted to Dr. C. P. Coogle for supplying the rat sarcomas used in Experiments 1–8. This tumor was propagated by transplanting an original spontaneous sarcoma encountered in the animal colony of the Anderson Hospital (AH). A detailed description of the tumor is forthcoming. Dr. W. A. Selle kindly furnished the mouse breast carcinoma (C_3H) and the methylcholanthrene-induced rat tumors. Dr. M. Bodansky made available the rat feti.

SUMMARY

Determinations of codehydrogenase I (Cozymase) were carried out on tumor tissues for the purpose of substantiating and supplementing current theories of metabolic peculiarities in malignant growth. Optimum conditions for the extractions of coenzyme and dihydrocoenzyme were elaborated. The codehydrogenase content of AH rat sarcoma, rat methylcholan-

threne tumor, and C_3H mouse breast carcinoma was found to be low. The excess dihydro-coenzyme found in Jensen rat sarcoma was not observed in the tumors listed above.

BIBLIOGRAPHY

1. Bernheim, F., and v. Felsoevanyi, A.: Coenzyme Concentrations of Tissues. *Science, 91*:76, 1940.
2. Burk, D.: *Some Fundamental Aspects of the Cancer Problem, A.A.A.S.* Publication, Section on Medical Science. New York, 1937.
3. v. Euler, H., Malmberg, M., and Guenther, G.: Die Biochemie des Jensensarkoms. *Z. Krebsforschung, 45*:425, 1937.
4. v. Euler, H., Schlenk, F., Heiwinkel, H., and Hoegberg, B.: Cozymase und Nikotinsaeureamid Gehalt im Tierkoerper und in der Hefe. *Z. Physiol. Chem., 256*:208, 1938.
5. Greenstein, J. P.: *Biochemistry of Cancer*, Academic Press, New York, 1947.
6. Jandorf, B. J.: The Stability of Diphosphopyridine Nucleotide in Rat Tissues, *J. Biol. Chem., 150*:89, 1943.
7. Krishnan, P. S.: Interference by ATP in the Estimation of Coenzyme I. *Science, 105*:604, 1947.
   Krishnan, P. S.: Oxygen Absorption Method for the Estimation of Coenzyme I. *Arch. Biochem., 16*:291, 1948.
8. Potter, V. R.: Biological Energy Transformations and the Cancer Problem. *Advances in Enzymology, 4*:201, 1945.
9. Potter, V. R., and Elvehjem, C. A.: A Modified Method for the Study of Tissue Oxidations. *J. Biol. Chem., 114*:495, 1936.
10. Potter, V. R., and Liebl, G. J.: Biocatalysts in Cancer Tissue. *Cancer Research, 6*:18, 1945.
11. Schlenk, F., in Bamann and Myrbaeck: *Methoden der Fermentforschung*, Thieme, Leipzig, 1941; Academic Press, New York, 1945.
12. Schlenk, F.: Nicotinamide Nucleotide Enzymes, in *A Symposium on Respiratory Enzymes*, Univ. of Wisconsin Press, 1942.
13. Schlenk, F.: Whither Enzyme Chemistry. *Texas Rep. Biol. Med., 2*:183, 1944.
14. Schlenk, F.: Enzymatic Reactions Involving Nicotinamide and Its Related Compounds. *Advances in Enzymology, 5*:207, 1945.
15. Schlenk, F., and v. Euler, H.: Cozymase; in Zechmeister, *Fortschritte der Chemie Organischer Naturstoffe*, Vol. 1, Springer, Vienna, 1938.
16. Schlenk, F., and Schlenk, T.: Notes on the Purification and Determination of Codehydrogenase I (Cozymase). *Arch. Biochem., 14*:131, 1947.
17. Stern, K., and Willheim, R.: *The Biochemistry of Malignant Tumors.* Reference Press, Brooklyn, 1943.
18. Warburg, O.: *Ueber den Stoffwechsel der Tumoren.* Springer, Berlin, 1926. Translated by F. Dickens, R. N. Smith Co., New York, 1931.

CORTICAL ATROPHY AS THE ETIOLOGICAL FACTOR IN CERTAIN TYPES OF MENTAL DISORDERS

JACK R. EWALT AND L. C. HANES*

Atrophy of the brain severe enough to produce mental symptoms is commonly caused by general paresis, senile deterioration, cerebral arteriosclerosis, hypertension or trauma. In addition to the above groups, there are the pre-senile dementias which are usually subdivided into Pick's disease, Alzheimer's disease and presbyophrenia.

The textbook descriptions of Pick's disease and Alzheimer's disease and the attempts to divide them clinically are rather confusing in that there are many overlaps in the symptoms described in the total literature on the subject. Edwards, noting the overlapping and contradiction found in the descriptions of these two conditions in the literature as well as the great similarity to the presenile dementias, proposed the hypothesis that the three dementias were simply varying manifestations of a single disease process. Stengel presents one of the largest series, consisting of ten cases of Alzheimer's and one case of Pick's disease, nine of whom were confirmed by post mortem examination. He too discussed the difficulty encountered in the differential diagnosis of the two conditions and attempted to explain some of the slight symptomatic differences on the basis of different anatomical involvement. He states that the underlying white matter is much more severely involved in the atrophic process in Pick's disease than in Alzheimer's disease. He also comments on the similarity of the symptomatology in a patient with Pick's disease and a patient with prefrontal lobotomy. It should be recalled, however, that when Pick described the condition in 1898 he presented the case of a 67-year-old woman who showed a slow but steadily progressing loss of memory and a speech disturbance with a preservation of automatic memory. This patient had no paranoid delusions, no bizarre actions, and no convulsive seizures,

*From The University of Texas Medical Branch, Galveston State Psychopathic Hospital, Galveston, Texas. Received for publication May 20, 1948.

which Pick thought set it apart from the other senile deteriorations. Pick also postulated that it was due to some kind of vascular disease superimposed on a senile involutional process. Polatin, Eisenstein and Barrera report two patients who had been hospitalized with paranoid dementia praecox for long periods of time before it was decided that the patients were suffering from some kind of organic brain disease, and pneumoencephalogram revealed marked cortical atrophy in the frontal and parietal regions on the right side in one case and the left side in the other. Both cases had cortical biopsies which showed slow progressive atrophic pathology in the nerve cells. Goldstein and Katz report that Pick's disease can be diagnosed on psychologic criteria alone. They report one case with marked atrophy in the frontal region of the cortex and they felt that the patient's behavior showed consistent good performance on tasks which can be performed by concrete behavior but failed in the task which could be fulfilled only by an abstract attitude. They felt that patients with diffuse lesions, such as Alzheimer's disease, would show a deterioration in the spheres of both concrete and abstract behavior. Kahn and Thompson also report that a close study of the symptomatology will enable one to make a clinical differentiation between Pick's and Alzheimer's disease. They believe that in Pick's disease the use of memory as an intellectual tool is impaired early. In Alzheimer's disease, on the other hand, memory itself is destroyed.

Lowenberg, Boyd and Salon present a case that started at 27 years with definite evidence of frontal, temporal and parietal lobe atrophy, and this case was characterized by convulsive attacks, spasticities, regidities, contractures, and twitching, in addition to difficulties in perception and difficulties in the recognition of the meaning and significance of stimuli. This case, while showing some of the neurologic findings, supposedly not present in Pick's disease, was confirmed by autopsy.

Hassin and Levitin report a case, confirmed by autopsy, in which the principal symptom was the patient's difficulty in handling concepts of any degree of complexity.

Davison reports two cases and concludes that early, severe memory defects occur in all spheres in Alzheimer's disease,

but in Pick's disease some retention of memory can be demonstrated. He also shows that the delusions, hallucinations, confabulations and seizures are more commonly seen in Alzheimer's disease. He discusses the pathogenesis of Pick's disease and suggests that it may be heredo-degenerative in type with the atrophy limited to the genetically younger areas of the brain. He also states that angiospasm, with resulting cerebral anemia, may play an important part in the atrophic process. Pick himself believed that the etiology probably was some type of vascular pathology added to beginning senile changes.

Malamud and Waggoner present three cases who are related to a case presented by Lowenberg, one being the younger brother of Lowenberg's case, and the other two being first cousins. They felt that the disease followed a dominant pattern of inheritance.

Akelaitis reports a case in which there is not only the mental deterioration and change of typical Pick's disease, but also a rather severe Parkinsonian syndrome. These changes were verified at post mortem. The changes were diffuse, involving the entire brain, but showing more atrophy of the caudate nucleus than any case previously reported in the literature. The putamen was reasonably well preserved. We believe it is obvious even in this sketchy review of the literature, that there is a great deal of overlapping and unclearness in the symptomatology ascribed to the presenile atrophies. The two points on which most authors agree are that cases with diffuse atrophy show severe, generalized memory loss, and patients showing focal atrophy present a loss of the abstract functions.

In our own series of cases we have ten patients varying from 26 to 60 years of age who show pneumoencephalographic changes typical of cortical atrophy of varying degrees. These patients have no vascular or other known pathology. Two additional cases show marked cortical changes but in these patients there is hypertension and some degree of arteriosclerosis. Before proceeding to a more detailed discussion of these patients, it should be pointed out that in each instance the patient was referred to us with what was presumed to be a functional mental illness, in most instances schizophrenia.

In attempting to summarize the findings in our twelve cases (Table I), it should be noted that patients showing marked confusion and disturbance in the sensorium in all spheres had,

TABLE I

	Memory	Hallucinations	Neuro.
Diffuse (6)	xxxxxx	xx	xxx
Focal (4)	x	xx	
H.T. (2)	xx	x	x

with one exception, generalized or diffuse cortical atrophy. The one exception had focal atrophy, and this particular patient (W.H.) had been ill two or three years. It will be noted that the other patients showing more discrete or focal atrophy tended to have a relatively clear sensorium and fulfilled in general the requirements for Pick's disease. It will also be noted that patients showing diffuse atrophy without hypertension show essentially the same symptoms as those with hypertension, and the pneumoencephalogram was the same in one hypertensive as in the diffuse atrophy group.

A. W.—52-year-old white female. Duration of illness five years. Complaint by family of memory loss, irritability, neglect of housework, withdrawing from friends, wandering and incoherent speech, fainting spells, and temper outbursts. In the hospital the patient was rather tense, restless, would frequently become disturbed and throw things. Physical examination was essentially normal. Neurological examination revealed the patient to have a rather stiff gait with absence of associated movements and a tremor of the fingers. The tremor was of the tension type. Mental status revealed the patient to be circumstantial, verbose, at times showing hysterical-like behavior and complaints. She would often give silly inappropriate answers. Facies appeared to be rather dull and apathetic. She expressed the delusion that she suffered from syphilis and stated that God spoke to her. Sensorium showed a marked disorientation for time and place. Poor memory for recent and remote events. Poor retention and recall. Spinal fluid examination was within normal limits. Pneumoencephalogram reported increased convolutional marking over the entire cortex, more marked in the frontal areas. E. E. G. showed abnormal record of borderline type. This patient was committed.

R. A. C.—60-year-old white female. Duration of symptoms three years. Family complained she had lost interest in her surroundings, in her housework, neglected her person, and had taken to drinking beer excessively. In the hospital, the patient was reasonably co-operative but at times would

become quite untidy and seclusive. She was extremely obese. Neurological examination was entirely normal. Mental status revealed a tendency to garrulous disassociated productions with some fabrications. She was markedly distractible. Many of her answers were irrelevant. At times she would become incoherent. Affect was marked by emotional instability and irritability. No hallucinations or delusions were produced. Sensorium revealed marked disorientation in time and place. Remote and recent memory were poor. Retention and recall were usually poor, but at times seemed good. Spinal fluid examination was normal. Pneumoencephalogram revealed diffuse cortical atrophy of rather marked degree. Discharged to family.

H. H.—33-year-old white female. Duration of symptoms three years. History of impulsive, silly outbursts. At times the behavior became quite immodest and immoral. Family complained of memory disturbance. In the hospital the patient was confused and untidy throughout her stay. Conversation frequently incoherent and irrelevant. In general patient was co-operative. Physical examination was negative. Neurological examination —deep reflexes were increased, more on the right than on the left, bilateral Hoffman and Babinski signs. Bilateral paling of the optic disc. Congenital squint in the left eye. Mental status revealed increased psychomotor activity. Speech was irrelevant. Moderate irritability. No hallucinations or delusions. Sensorium showed marked defects in remote and recent memory. Patient was disoriented as to time and place, and retention and recall were poor. General information was poor. Spinal fluid showed a protein of 50 mgms./100 cc's, otherwise normal. Pneumoencephalogram revealed mild diffuse cortical atrophy. E. E. G. revealed diffuse disturbance suggesting a mild convulsive disorder. Pneumoencephalogram three years before was normal.

O. D.—44-year-old male. Duration of illness one month. Patient entered with a history of a moderate head injury one month prior to entry into the hospital. The patient became alcoholic, hyperactive, talkative, extremely confused and cut his head severely by running it through a window. On admission to the hospital the patient was extremely hyperactive. General physical and neurological examinations were entirely normal except for the lacerations on the scalp. Mental status revealed marked flight of ideas and distractibility with confabulations and much irrelevant incoherent talk. He was extremely happy and euphoric. Sensorium revealed the patient to be disoriented for time and place. Remote and recent memory were badly impaired. General information and calculation were poor. Judgment and insight were poor. Spinal fluid examination revealed a protein of 60 mgms. on admission and seventeen days later the protein was 40. Pneumoencephalogram showed dilation of the third and fourth ventricles. Subarachnoid spaces were not completely filled. There was also an old fracture of the right occipital and temporal bones. Electroencephalogram showed diffuse changes.

L. D.—52-year-old female. Duration of illness two years. The patient had been bedridden for the past year. The family complained that she was confused, had nervous jerking spells. In the hospital the patient had several episodes with twitchings of the right side and two generalized seizures. She was confused but generally co-operative. Neurological examination revealed increase of the deep reflexes on the right side. Abdominals were present. Babinski group was negative. There was also hyperesthesia on the right side and patient had a slurred speech. Mental status examination revealed some emotional ability and a marked sensorium loss. Spinal fluid reports were normal. Pneumoencephalogram showed a marked porencephaly with an air pocket in the left parietal lobe and rather poor filling of the subarachnoid spaces.

A. A.—47-year-old female. Duration of symptoms five months. History is that the patient ran away from home, lost her temper, got into fights with the family and with strangers. In the hospital she was extremely irritable and argumentative with the other patients. General physical examination revealed a hypertension of 235/118 and evidence of generalized arteriosclerosis. Neurological examination was entirely negative. Mental status revealed a flight of ideas, marked distractibility and many incoherent productions. Patient had definite paranoid delusions, feeling that other people were stealing from her and attempting to poison her. She also expressed grandiose ideas stating that she was the strongest person in the world and that she could fly down to the ground or up on the roof. Sensorium was disturbed, showing disorientation in time and place, defects in recent and remote memory, retention and recall. Judgment and insight were very poor. Spinal fluid was entirely normal. Pneumoencephalogram revealed generalized diffuse cerebral atrophy.

M. H.—53-year-old female. History rather unsatisfactory, family stating she first became ill three weeks prior to admission. History revealed she was confused, agitated, talked to inanimate objects, ate very poorly, unable to sleep at night, unable to distinguish between her three children. In the hospital she was mute, unco-operative, excreta careless, ate anything including pieces of bed clothing, ate talcum powder, and on several occasions ate bits of furniture. She had two convulsions on the ward. General physical examination revealed blood pressure to be 150/110, and traces of albumen and casts in the urine. While in the hospital patient developed a thrombophlebitis in the left leg and was febrile at that time. The neurological examination revealed some hyperactivity in the Achilles and Knee Jerks and the Babinski was positive bilaterally. The rest of the examination was essentially normal. Mental status examination revealed the patient to be mute. During her entire stay in the hospital she said very few words and these were noted to be "No" and "Uh Uh." Patient appeared to be quite apathetic and vegetating. Sensorium couldn't be evaluated as the patient wouldn't co-operate. Attempts to evaluate the sensorium under amytal were unsuccessful. Spinal fluid examination was all within normal limits. Pneumoencephalogram revealed little air in the subarachnoid

spaces. Ventricles were normal in size and configuration. (A tentative diagnosis of adhesive arachnoiditis was made.) Patient died in her third hopsital week. Autopsy revealed marked diffuse cortical atrophy with many small areas of softening. She also had terminal broncho-pneumonia.

W. H.—54-year-old white male. Duration of illness two to three years. Memory extremely poor. Patient was unable to care for self or work. He forgot to eat, wandered around, walked across the street in front of automobiles and trucks. In the hospital the patient was co-operative but his memory was so bad that he couldn't find his way to and from the bathroom and dining room. He was usually polite, cheerful and friendly. General physical examination revealed a mild peripheral arteriosclerosis with normal tension. Neurological examination was entirely normal. Mental status revealed the patient to be rather unproductive. Many of his remarks were irrelevant. He seemed rather cheerful and friendly, but not too aware of what was going on around him. He was rather apathetic most of the time. No evidence of hallucinations or delusions elicited. Remote and recent memory were poor. Retention and recall were poor. He had very little insight or judgment. Spinal fluid, normal. X-ray revealed marked separation of the convolutional folds with more atrophy in the left parietal occipital area. There was also accumulation of air over the frontal regions and over the basal cistern.

H. D.—43-year-old white male. Duration of illness four to five years. He complained of headaches, short periods of irrational behavior followed by amnesia. Family complained that patient frequently shaved twice, one time right after another. At times, he shaved one side of his face twice and forgot to shave the other side. On one occasion he lost his car. He sold some cows and then thought they had been stolen. On the ward the patient was co-operative, friendly, sociable, but rather untidy about his person. General physical and neurological examinations were both entirely normal. Mental status revealed history of mild depressive ideas, but these were not present while he was in the hospital. No evidence of hallucinations or delusions. Patient was oriented. His memory was fair for remote and recent events. He was not able to use his memory in a positive way. He could recall things given him to recall immediately, but would be unable to remember to go to his meals, to shave or dress unless prompted to do so. Spinal fluid examination was entirely normal. Pneumoencephalogram revealed widening of the convolutional markings throughout the frontal areas. The widening was mild in degree and rather diffuse. Electroencephalogram was normal.

W. H.—50-year-old white female. Duration of symptoms four years. History of intermittent episodes in which the patient would lose interest, become depressed, slovenly, incontinent of urine and at times stuperous. At other times she would become hyperactive and talkative. The patient was admitted to the hospital as a manic. In the hospital the patient was unco-operative, had to be tube fed most of the time, spent a great deal of time in bed. Physical examination revealed obesity and no other changes

from normal. Neurological examination revealed no abnormalities. Mental status—patient talked in a rather incoherent, irrelevant manner. Showed increased productivity. She was rather apathetic but at times would become irritable. She had auditory hallucinations, God telling her what to do, with paranoid ideas of people trying to put an anesthetic on her nose. She was oriented for time and place. Recall and recent memory were poor. Patient had difficulty in remembering to dress. She would forget to go to the bathroom, would forget her way to the day room, but on ordinary testing would respond normally. Spinal fluid examination was normal. Pneumoencephalogram revealed atrophy of the cerebral cortex which was more marked over the right frontal and parietal lobe. Ventricular system showed some diffuse enlargements.

G. M.—59-year-old white female. Duration of illness unknown. Thought to be only a few months. There was a history of weight loss, numerous somatic delusions. Patient spent days in bed. In the hospital she spent most of her time in bed. After some elecric shock she became hyperactive and noisy. She would wander from room to room, and smeared feces on the walls and on her person. Physical examination revealed the patient to be emaciated and have pigmentation and scarring over the lower extremities which appeared to be secondary to varicose veins. Neurological examination was entirely normal. Mental status revealed much spontaneous speech, most of it being irrelevant and at times incoherent. She was extremely evasive. At times she would stay in bed and at other times she would be generally disturbed and excreta careless. Patient was apathetic. She had numerous nihilistic delusions, thinking she was dead, had no stomach, no intestines, no blood and no veins. She was oriented as to time and place. Judgment and general information and insight were rather scanty. Spinal fluid was entirely negative. Pneumoencephalogram showed small areas of widening of the cortical pathways in the fronal region bilaterally. Electroencephalogram was unsuccessful.

C. H.—26-year-old white male. Duration of symptoms three years. There was a history of frontal headaches and momentary losses of vision. The attacks of blindness lasted about five minutes. There was loss of vision and complaint of flashing red and green lights. In the hospital patient was co-operative, pleasant and neat. Physical examination was normal. Neurological examination was normal. Mental status revealed patient was markedly apathetic with mild, poorly defined paranoid delusions. Sensorium was poor for general information but was otherwise intact. Spinal fluid examination was normal. Pneumoencephalogram showed some blunting of the anterior horns of the lateral ventricles and increased accumulation of air over the left hemisphere suggesting mild left cerebral atrophy. Electroencephalogram showed bilateral frontal irritation of convulsive type. Patient was placed on Dilantin and these attacks of headaches and blindness cleared up. The rest of the mental status picture remained unchanged.

Discussion

In the above cases the presence of severe diffuse cortical atrophy invariably resulted in marked disturbance in behavior and in the intellectual processes irrespective of etiology. On the other hand, the presence of focal areas of atrophy produced changes in the intellectual processes not so immediately obvious, which must be demonstrated by special forms of testing and extremely careful observation. It is to be noted, however, that one of the patients showing localized change showed symptoms suggestive of diffuse pathology, and two cases with minimal diffuse pathology showed no change in the ordinary sensorium examination.

On the basis of these studies one might state that the degree of intellectual change shown by the patient will be dependent upon the total amount of cortical loss present, rather than upon the particular area involved. This seems to be true within wide limits but patients in the early phases of frontal lobe atrophy show alterations in abstract attitudes which are obvious on careful testing. The symptomatology of these patients often resembles the psychoses of the schizophrenic type, who also have disturbance in abstract behavior. It is believed that patients suffering from one of the schizophrenias or schizophrenic-like disorders of the acute confusional type must be carefully studied if patients with cortical atrophy are to be excluded from the group. Much more detailed and varied clinical and psychologic studies of the intellectual function of patients of this type should be made. The work of Halstead on neurosurgical cases should furnish a valuable baseline for comparison in such a study.

Conclusions

(1) Twelve cases of brain atrophy are presented, all of whom came to the hospital presenting complaints resembling those of schizophrenic or manic psychoses.

(2) Two patients showed changes suggestive of Alzheimer's disease, but in the presence of hypertension.

(3) Six of these cases showed mental changes typical of Alzheimer's disease and without any evidence of other pathology to explain the conditions.

(4) Four cases showed evidence of Pick's disease without other evidence of pathology to explain the condition.

It is believed that brain atrophy is often overlooked as the etiologic factor in the psychoses. The electroencephalograph is helpful in diagnosing these cases, but is not absolutely dependable. Pneumoencephalograms seem the method of choice. Patients not showing intellectual changes that are immediately demonstrable but who have an organic appearance about them should be re-examined in greater detail for the degree of function of the intellect. If this is impaired, pneumoencephalography is indicated.

BIBLIOGRAPHY

Akelaitis, Andrew J.: *Atrophy of Basal Ganglia in Pick's Disease—A Clinicopathologic Study*, Arch. Neuro. and Psychiat., *51*:27–34, January, 1944.

Davidson, Charles: *Circumscribed Cortical Atrophy in the Presenile Psychoses—Pick's Disease—A Clinicopathologic Study*, Am. J. Psychiat., *94*:803–818, January, 1938.

Edwards, A. T.: *Presenile Dementia: A Brief Review*, Med. J. Australia, *1*:248–249, March 20, 1943.

Goldstein, Kurt and Katz, Siefgried E.: *The Psychopathology of Pick's Disease*, Arch. Neuro. and Psychiat., Vol. 38, September, 1937, p. 473.

Hassin, George B., and Levitin, David.: *Pick's Disease—Clinicopathologic Study and Report of a Case*, Arch. Neurol. and Psycriat., *45*:814–833, May, 1941.

Kahn, Eugene, and Thomposn, Lloyd, J.: *Concerning Pick's Disease*, Am. Jr. Psychiat., Vol. *13*:937–946, March, 1934.

Lowenberg, K.: Boyd, David, A., Jr., and Salon, D. D.: *Occurrence of Pick's Disease in Early Adult Years*, Arch. Neurol. and Psychiat., *41*:1004–1020, May, 1939.

Lowenberg, K.: *Pick's Disease—A Clinicopathological Constribution*, Arch. Neuro. and Psychiat., *36*:768–689, October, 1936.

Malamud, Nathan, and Waggoner, Raymond W.: *Genealogic and Clinicopathologic Study of Pick's Disease*, Arch. Neuro. and Psychiat., *50*:288–303, September, 1943.

Polatin, Phillip, Eisenstein, Victor W., and Barrera, S. Eugene: *Organic Organic Psychoses Simulating Dementia Praecox, A Report of Two Psychoses Simulating Dementia Praecox, A Report of Two Cases with Brain Biopsy Studies*, Psych. Quart., *18*:391, July, 1944.

Stengel, E.: *A Study on the Symptomatology and Differential Diagnosis of Alzheimer's and Pick's Disease*, J. Ment. Sc., *89*:1–20, January, 1943.

DOES LIGATION OF PERIADRENAL TISSUES PRODUCE ELEVATION OF BLOOD PRESSURE?[1]

ERIC OGDEN, ELEANORE TRIPP, W. DOYNE COLLINGS* AND JOSEPH VICTOR†

Introduction: Victor (1) reported in 1945 that unilateral periadrenal ligation of blood vessels and tissues in six dogs was followed by elevation of systolic and diastolic blood pressure within one to three days. An attempt in Galveston (E. O. and W. D. C.) to repeat the experiments upon five dogs was unsuccessful (Table I).

A number of workers in other laboratories have also made attempts to repeat the original observations but have failed. Among these are Goldblatt (2), Page (3), Maaske (4), Holman (5) and Wakerlin (6). In view of the lack of success in repeating the work, it seemed imperative that an attempt be made to eliminate differences of technique.

Technique: The description of the operation in the original report did not sufficiently emphasize the necessity for using heavy silk ligature and for taking a wide and deep bite of periadrenal tissue. The operations on dogs in Galveston (Table I), had been performed through a posterior approach with incisions in the periadrenal tissue. On the other hand, the operation carried out in the New York laboratory employed a transperitoneal approach through an antero-lateral, subcostal incision. This avoided periadrenal trauma, except that produced by the ligatures in the adrenal area. Accordingly, nine experiments

[1]From the Carter Physiology Laboratory, The University of Texas Medical Branch, Galveston, Texas, and Research Service, First (Columbia) Division, Goldwater Memorial Hospital, Department of Hospitals, and the College of Physicians and Surgeons, Columbia University, New York City. Received for publication June 28, 1948. Supported in part by grants from the Life Insurance Medical Research Fund to Columbia University College of Physicians and Surgeons and from the John and Mary R. Markle Foundations to The University of Texas Medical Branch.

*Present Address: State University of Iowa, College of Medicine, Iowa City, Iowa.

†Present Address: Pathology Branch, Research and Development Department, Camp Detrick, Frederick, Maryland.

TABLE I

Influence of left periadrenal ligation of blood vessels and tissue on the blood pressure of dogs.

Dog	Before Operation		After Operation													
			1 Day		2 Days		4 or 5 Days		1 Week		2 Weeks		2 Months		3 Months	
	BP	PR	BP	PR	BP	PR	BP	PR	BP	PR	BP	PR	BP	PR	BP	PR
1			115	90	88	88			98	72						
2	100	68	100	96	105	80	95	68	108	66						
3			115	78	97	88	92	66	95	60	110	65	95	68	90	60
4			125	90	130	160	118	120	122	104						
5					120	115	116	105	110	90	135	150				

PR—Pulse Rate.

BP—Blood Pressure measurements on unanesthetized dogs made by puncture of the femoral artery with a needle connected to a Tycos manometer. The lowest readings are recorded. We have evidence that readings so made approximate diastolic blood pressure. Operations in Galveston.

were performed in Galveston by the authors of this paper following the operative technique originally described. These experiments appear in Table II in the order in which the operations were done and the initials of the investigators performing the surgery indicate that the operations were an adequate repetition of those in the original report.

The blood pressure was measured by palpation (1), by direct puncture with a needle connected to a Tycos manometer or by puncture with a needle connected to an optical manometer, (glass spoon 7).

Careful study of the differences of technique in the handling and measurement of animals in the Galveston and New York laboratories revealed no essential differences; and the staffs of both laboratories are in complete agreement that the optical measurements of diastolic pressure and the pulse rate determinations made in the two locations are certainly equally representative of the functions they purport to measure, are accurate, and relatively stable. Precise measurements of systolic pressure, however, are notoriously uncertain and this figure is subject to more chance variation than diastolic pressure. For these reasons the diastolic measurements are regarded as of great importance.

The dogs in New York though quiet and well-trained while on the animal board were more active and demonstrative when not on the board than the dogs in Galveston.

Findings: The data from the nine experiments presented in Table II show occasional temporary elevations of systolic pressure, but the blood pressure of the animals did not behave like that of the animals in the original report. In the sixth, seventh and eighth months three of the dogs showed a diastolic blood pressure greater than 100 mm. Hg. All the figures should be evaluated in connection with the pulse rate values since the pulse rate usually rose after the operation, and may perhaps indicate that the dogs were less calm. Furthermore, these three dogs (Nos. 205, 206, 211) seemed to become temperamental and more difficult to handle at this time. Seven of the operated animals were shipped after about a year to Dr. Victor in Maryland where their blood pressures were recorded with a Hamilton manometer and they were immediately subjected to morphological examination.

TABLE II

Influence of left periadrenal ligation of blood vessels and tissue on the blood pressure of dogs.

Dog	Before Operation Tycos BP	PR		After Operation 1st Month Tycos Palp.* BP	PR	2nd Month Palp. BP	PR	3rd Month Optical BP	PR	6th Month Optical BP	PR	7th Month Optical BP	PR	8th Month Optical BP	PR	14th Month‡ Optical BP	PR
208	107 (11)	76	(JV,EO)	95 (7)	115 (13)	64	130 (5)	68	130/87 (4)	76	146/80 (5)	90†	164/78 (3)	85	173/84 (2)	102	181/100 (1)	92
207	101 (9)	81	(JV,EO, WDC)	101 (6)	115 (12)	71	137 (3)	56	131/72 (4)	81	160/86 (3)	118†	150/82 (3)	118	161/88 (2)	110	159/74 (1)	80§
205	108 (13)	81	(EO,JV)	109 (4)	150 (8)	69	130 (5)	69	129/79 (4)	89	182/96 (4)	129	168/91 (3)	140	208/101 (2)	138	259/141 (1)	104
211	126 (14)	111	(WDC,JV)	105 (5)	101 (7)	96	141 (3)	104	142/89 (4)	151	185/109 (6)	156†	204/132 (3)	176	166/103 (2)	176	241/136 (1)	124
206	121 (9)	97	(EO,JV)	110 (5)	160 (11)	89	175 (4)	80	155/74 (4)	109	206/97 (3)	122	208/109 (2)	164				§
209	118 (12)	102	(WDC,JV)	111 (5)	129 (10)	102	131 (5)	79	168/85 (4)	94	173/81 (5)	85†	167/92 (3)	120	166/85 (2)	83	106/58 (1)	108§
210	96 (8)	105	(EO,ET)	115 (1)	108 (5)	74	135 (3)	77	155/89 (4)	124	156/83 (4)	145	184/93 (3)	166	166/103 (2)	176		
6	138/71 (9)	109	(EO,ET)	128/65† (4)		65	154/70 (1)	116	133/68 (4)	115	157/79 (4)	129	170/84 (1)	128‖				
7	153/80 (5)	99	(EO,ET)	175/93 (9)		113	181/91 (2)	122	162/83† (2)	118‖								

Figures in parentheses tell the number of determinations averaged. Initials indicate operator (first) and those assisting or present. *Palpation method as described by Victor (1). †Microfilaria detected in blood at this time. ‡Fourteenth month measurements made immediately after shipment to Maryland. §Microfilaria detected in blood at autopsy. ‖All measurements on these two dogs were optical. The boxed numbers refer to measurements made in the fourth and fifth months respectively. Operations in Galveston.

Considerable periadrenal scarring was present on the side of operation in all seven dogs which were examined. Arteries and veins, some thrombosed or obliterated, as well as nerve fibers and ganglia were included in the scars about the ligatures. In the cortices of six of the seven operated adrenals, the concentration of histologically demonstrable cholesterol, cholesterol ester and ketosteroids (8) was greater than in the contralateral adrenals. The exception was No. 211. Neutral fat concentration in adrenal cortical cells or chromaffinity of medullary cells were not altered by the operation. Microfilaria appeared in blood or tissues of all dogs except Nos. 211 and 205, although No. 211 had shown microfilaria in its blood eight months before autopsy. Microfilaria almost filled the dilated and hypertrophied right ventricles and pulmonary aorta of No. 206. Endarteritis of the pulmonary arteries was present in this case, a lesion characteristic of heart worm infestation in the dog.

Glomerular changes which are unique in our experience were found in the kidneys of No. 205. Most glomeruli were unaltered. However, scattered ones showed hypertrophy, increased nuclear number and thickened and fibrotic Bowman's capsule. A few glomeruli had colloid droplets within epithelial cells of the tufts and of those lining thickened Bowman's capsules. Occasional glomerular adhesions but no crescents were seen. Except for rare clusters of lymphoid and mononuclear cells in positions unrelated to altered glomeruli, no cellular infiltration was found in the cortex although the interstitial tissue of the cortex was increased in amount and quite acellular. Many collecting tubules of the medulla contained albuminous granular or hyalin casts. Blood vessels of all types were unaltered. The glomerular changes were suggestive of subacute glomerulo-nephritis but the number of glomeruli involved was slight. In all other dogs the kidneys showed no significant changes.

Pathological examination revealed nothing else, except infestations by various worms.

In the New York laboratory a further four dogs were subjected to the operation (J. V.) and the results were in essential agreement with those of the original report (Table III) except that the elevation of blood pressure in two instances was only temporary.

TABLE III

Influence of left periadrenal ligation of blood vessels and tissue on the blood pressure of dogs.

Dog	Before Operation		After Operation							
			1 Month		2 Months		3 Months		4 Months	
	BP	PR	BP	PR	BP	PR	BP	PR	BP	PR
392	189/87 (6)	106	225/95 (4)	106	235/98 (3)	112	240/115 (4)	112	249/119 (5)	113
*	195/93 (7)	106	259/108 (5)	96	295/115 (2)	102	286/129 (3)	116	243/130 (1)	132
408	180/97 (7)	144	202/123 (5)	141	211/98 (1)	125	218/92 (4)	132	193/92 (2)	143
†	194/85 (3)	135	218/94 (3)	139	250/105 (4)	133	246/119 (4)	145		
393	208/91 (4)	98	224/97 (3)	103	231/108 (4)	94	219/94 (3)	95	190/78 (2)	79
395	202/95 (3)	117	217/107 (4)	112	218/119 (4)	130	249/120 (3)	129	226/117 (4)	149

*Ligation of right adrenal 6 months after removal of left. Removal of ligated left adrenal was followed by normal blood pressure after three months.

†Ligation of right adrenal 5 months after operation on left.

Operations in New York. Figures in parentheses tell the numbers of observations averaged.

Discussion: When pariadrenal tissue ligation follows the technique originally described it is commonly followed by a slight elevation of diastolic blood pressure and a considerable elevation of systolic blood pressure and the pulse rate tends to rise. The rise in diastolic pressure is definite in seven of the thirteen animals here reported which have been subjected to this procedure (Tables II and III). Because diastolic pressures may be easily measured with a high degree of reliability and are not subject to chance fluctuations in animals which are carefully trained and carefully handled, this slight rise of diastolic pressure probably deserves further investigation.

The systolic blood pressure, on the other hand, was more strikingly and more often elevated but the instrumental difficulties involved in precise measurement of systolic pressure together with the extreme lability of this function make these rises difficult to interpret.

The blood pressure changes may occur immediately or may be delayed and when they occur they may be sustained or temporary.

It is possible that the tendency for increased pulse rate and increased systolic blood pressure to occur after this operation which involves scarring in the region of the adrenal gland and also in a region rich in sympathetic nerve fibers, should be correlated with the chance observation that some of these animals seemed to be more excitable after than before the operation.

The changes in blood pressure which appeared irregularly in the dogs operated in Galveston (Table II) seem to occur more definitely and regularly in those operated in New York (Table III and Victor's original report). The numbers involved are such that this may be a coincidence but the possibility that this represents a real difference must be considered.

The New York dogs' blood pressures did not fall when they moved south to Maryland. This suggests that climatic change does not account for the differences in behavior of the blood pressure. Furthermore, it seems likely that the dogs used by Dr. Goldblatt and Dr. Page in Cleveland and Dr. Maaske in Denver might have reacted to climate in a way comparable to the dogs in New York.

A dietary difference might underlie these phenomena. The New York dogs, which appeared to be in excellent health, were receiving a diet of Spratt's dog chow. The Galveston dogs, whose health appeared to be good, were held in weight balance or slight weight gain with Cowgill No. 3 diet (8). During the last half of the experiment the Cowgill diet was alternated with hospital scraps.

A final possibility to explain the differences is to attribute them to the effects of filaria infestation. A large proportion of dogs in the Galveston area are so infested (see Table II), but the disease is relatively rare in the animals in New York. However, dogs may be made hypertensive by the Goldblatt procedure in the Galveston area in spite of infestation with filaria. The dog (No. 211) showing the highest blood pressure reading obtained in Galveston had filaria in its blood at the time that these high blood pressure readings were made. It seems that filaria infestation is probably not a determining factor in this matter though the possibility is not completely excluded.

Conclusions: Many laboratories were unable to confirm the results of Victor (1945) partly because the description did not sufficiently emphasize the necessity of taking a wide and deep bite of tissue and of using a heavy ligature. Moreover, the elevation of blood pressure is often delayed or transient and since the greatest pressure change is systolic some of the investigators may have produced blood pressure elevation and have failed to observe it. Changes would be missed unless the measurements were made frequently over a long period of time and with equipment suitable for detecting changes in systolic blood pressure.

The immediate and sustained elevation of blood pressure in every one of the dogs in the original report was due to chance.

The accumulation of data on further dogs shows that the change does not appear in all the animals and is not usually great.

The mechanism of the elevation is still completely unknown and must await further investigation.

Summary: Three series of dogs (18 animals) have been subjected to two different procedures each involving the ligation

of part of the blood supply to one adrenal gland. When the procedure follows that of the original report it is sometimes followed by a slight elevation of diastolic blood pressure (definite in not more than seven of the thirteen animals, Tables II and III) and a considerable elevation of systolic blood pressure. The blood pressure changes may be immediate or delayed, sustained or temporary. The pulse rate tends to become elevated.

No explanation is offered for the phenomena.

REFERENCES

1. Victor, Joseph: Hypertension Produced in Dogs by Unilateral Ligation of Periadrenal Blood Vessels and Tissue, Proc. Soc. Exper. Biol. and Med., *60*:332, 1945.
2. Goldblatt, Harry: The Renal Origin of Hypertension, Physiol. Rev., *27*:120, 1947.
3. Page, I. H.: Personal Communication.
4. Maaske, Clarence A.: Personal Communication.
5. Holman, Russell: Personal Communication.
6. Wakerlin, George: Personal Communication.
7. Visscher, Maurice B., Kubicek, W. G., and Sedgwick, F. P.: Adaptation of the Glass Spoon Manometer to Physiological Studies, Rev. Sci. Instruments, *12*:101, 1941.
8. Bennet, H. S.: The Life History and Secretion of the Cells of the Adrenal Cortex of the Cat, Am. J. Anat., *67*:151, 1940.
9. Cowgill, George R.: Studies in the Physiology of Vitamins: II. Parenteral Administration of Vitamin B Mammalian Experiments, Am. J. Physiol., *66*:164, 1923.

REPORT OF CASE OF PRIMARY PAPILLARY ADENOCARCINOMA OF DUODENUM

With Special Reference to X-ray Study*

Jesse B. Johnson

Incidence. Primary carcinoma of the duodenum is a rare disease. According to Feldman, the incidence is 0.003% of all necropsies and 0.005% of all hospital admissions. In 30,000 roentgenographic studies of the gastrointestinal tract only one case was found. Raiford found eighty-eight benign and malignant tumors of the small intestine in 11,500 postmortem and 45,000 surgical cases at Johns Hopkins Hospital. Twenty-one tumors of the duodenum were found; of which only seven were carcinomata.

Age and Sex. The condition occurs between the fourth and sixth decades with a preponderance in the male sex. In 36 collected cases, according to Feldman, there were 24 males and 12 females.

Site. Carcinoma of the duodenum is classified topographically according to site. Supra-ampullary lesions occur in 15%, peri-ampullary in 65% and infra-ampullary in 20% of all cases. The lesions above the ampulla and beyond the pylorus are usually small, tend to ulcerate early, encircle the duodenum, encroach upon the lumen, and produce early symptoms as well as X-ray evidence of obstruction. The peri-ampullary type arise in or near the papilla and tend to encircle or extend along the duodenum. This type produces biliary and pancreatic obstruction with dilatation of the ducts, gall bladder with enlargement of the liver and pancreatic atrophy. In this area the point of origin may be the duodenum itself, the opening of the pancreatic or biliary ducts. The infra-ampullary type, which includes this case, arises between the ampulla and the duodenajejunal flexure. In this area they are often flat and broad, fre-

*From the Department of Radiology, The University of Texas Medical Branch, and the John Sealy Hospital, Galveston. Received for publication June 12, 1948.

quently ulcerate and produce stenosis with proximal dilatation. In the present case there were numerous small papillary and larger polypoid growths filling the post-ampullary portion of the duodenum.

Pathology. Grossly carcinomata of the duodenum may occur as polypoid or infiltrating growths. They are usually adenocarcinomas. Other histological forms do occur. The lesions tend to encircle the wall, narrow the lumen producing stenosis and proximal dilatation. Ulceration followed by constriction is not uncommon. Metastasis occurs late to the liver, regional lymph nodes, pancreas and lungs. Ulceration into the biliary tract with fistula is occasionally seen. Large sized ulcers are sometimes seen. The lesions are probably malignant from the beginning. An ulcerating carcinomatous lesion may be mistaken for benign ulcer. A palpable mass is said by Feldman to exist in about 35% of duodenal carcinomas.

Roentgen Diagnosis. The roentgen study offers the only method of identifying the lesion before operation. The diagnosis is made by observing the distortion of the normal roentgen anatomy of this segment of the bowel. The duodenal cap is normally smooth like the pyloric end of the stomach. The rugae run parallel with the lumen of the bowel from the apex of the cap to the ampulla of Vater. The ampullary area is easily identified by the end of the parallel rugae and the beginning of the transverse rugae or so called valvulae conniventes. The infra-ampullary portion has easily visible transverse rugae from the ampulla to the duodenojejunal junction. The supra-ampullary lesions are most likely to be interpreted as ulcer. Deformities of the mucosal pattern with stenotic findings may lead to the proper interpretation. Carcinomas arising around the ampulla do not obstruct the duodenum often but are more likely to obstruct the ducts.

The roentgen signs of carcinoma of the duodenum are : (1) annular infiltrating or ulcerating defect; (2) mucosal changes such as effacement and thickening of the mucosa; (3) irregular polypoid filling defects which narrow the lumen; (4) dilatation of the duodenum above the constriction with retention; (5) rigidity of duodenum wall; (6) palpable mass at the site of

obstruction or defect; (7) obstruction, and (8) dilatation of the stomach with gastric retention.

Differential Diagnosis. In considering the differential diagnosis of duodenal carcinoma, simple ulceration, ulceration with obstruction, pyloric carcinoma, carcinoma of the head of the pancreas, inflammatory masses and duodenum ileus must be considered.

Case Report

C. C., a 67 year old colored male longshoreman, entered the hospital December 16, 1947 for the fourth time. These previous admissions were not related to his present illness. On the last admission he came to the surgical service with an anal fistula and an inguinal hernia. This was to have been repaired, only it was noted there was marked anemia and the patient was referred to medical service for that reason. The blood studies

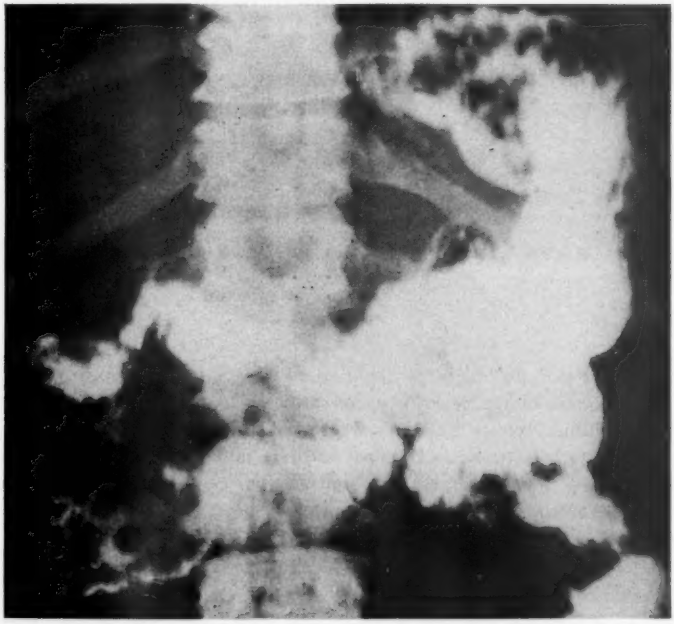


Fig. 1. Survey film, normal stomach. Duodenum shows massive filling defects, irregular and ragged in outline, greatly deforming lumen from ampullary region well into the ascending limb.

were as follows: r.b.c. 2.4 m. Hb 6.2 grms. Occult blood was present in the stools repeatedly with the patient on a meat free diet. Dr. W. C. Levin, the hematological consultant interpreted the anemia to be due to chronic blood loss and advised diligent search for the source of bleeding. Physical examination did not disclose any source of the bleeding. The adbdominal examination revealed only slight liver enlargement. X-ray studies showed the following: (See Figures 1 and 2.) The stomach and pylorus were

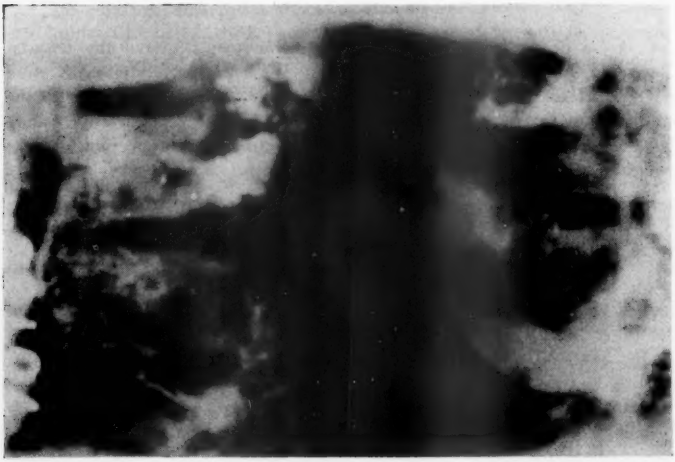


FIG. 2. Spot films showing essentially the same findings under compression.

normal. From the region of the ampulla through the descending limb and a portion of the ascending limb, multiple small and large irregular ragged filling defects were observed in the duodenum. These defects appeared to be intrinsic rather than extrinsic filling defects. This portion of the organ was dilated and the large and small defects stood out boldly. It was believed that they were intrinsic cauliflower types of defects. There were no obstructive changes and no one had ever palpated them. The reason for their not being palpable is revealed in the surgical and pathological findings.

The patient was operated upon by Dr. Albert O. Singleton, Jr., who made the following observations: "Many dense upper abdominal adhesions, liver normal, gall bladder thickened, shrunken and buried in the liver,

the common duct opened, catheter introduced and blood encountered on withdrawal from the duodenal end. From the outside of the duodenum, no pathology could be detected except for soft friable papillomatous masses within. Upon opening the duodenum many soft friable papillomatous masses were seen. They extended from the end of the first portion well into the third portion. The duodenum was resected, the common duct anastomosed to the jujunum and gastro-jejunostomy performed."

Dr. H. W. Neidhardt interpreted the gross and microscopic specimens as follows: (1) papillary adencarcinoma of the duodenum. (2) multiple polyps of the duodenum showing malignant transformation (Figures 3 and 4). The patient was discharged from the hospital after two weeks in good condition. The patient returns to the out clinic for regular observation and is doing well at the present time.

FIG. 3. Photograph of the gross specimen shows the massive cauliflower papillomatous adenocarcinoma of the region.

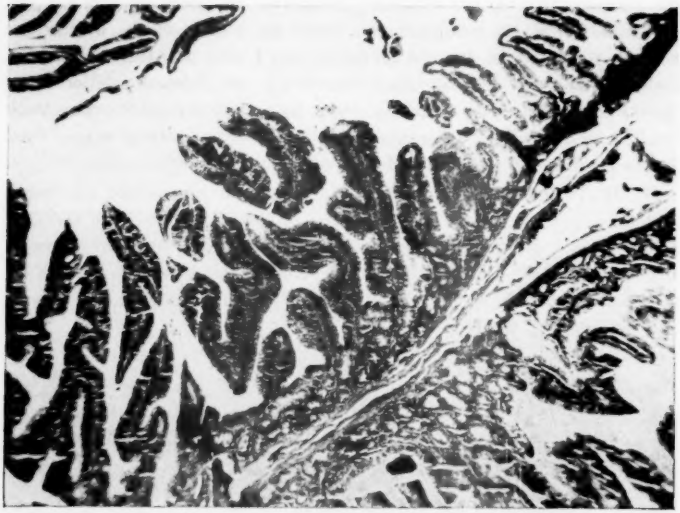


FIG. 4. Microscopic specimen shows the malignant changes near the ends of the folds.

SUMMARY

A case report of primary carcinoma of the duodenum has been presented. Brief reference was made to the clinical features. Detailed description of the roentgenographic changes have been given. The surgical and pathological findings have been reported and four photographs of roentgenographic and pathological material have been included.

REFERENCES

Feldman, Maurice: *Clinical Roentgenology of the Digestive Tract*, Williams and Wilkins Co., Baltimore, 1945.

Raiford, T. S.: *Tumors of Small Intestines.* Arch. Surg., *25*:321–355, 1937.

THE INHIBITORY EFFECT OF ANTIORGAN SERA ON EXPERIMENTAL RICKETTSIAL INFECTIONS IN THE PRESENCE OF TESTICULAR EXTRACT*

LUDWIK ANIGSTEIN AND DOROTHY M. WHITNEY
WITH TECHNICAL ASSISTANCE OF NORMA W. HANSEN

Our recent studies have shown that guinea pig antiorgan immune serum can prevent or suppress typhus and spotted fevers when both inocula were given intradermally. Furthermore, the recovered guinea pigs proved to be immune to reinoculation with the homologous virulent rickettsiae (Anigstein, Whitney and Beninson, 1948). At that time, the two-phase operation taking place within a restricted area of the guinea pig dermis was emphasized. It was presumed that the resistance of the dermal barrier, particularly changes in its permeability, played an active part in this effect.

Further analysis of the interaction of the antiorgan sera and rickettsiae was attempted in the present study using subcutaneous injections of both antiorgan serum and rickettsiae thus by-passing the dermal barrier. The site of infection was either distant from the site of serum inoculation, or followed the serum within the same area. Attempts were made to enhance the diffusion of the serum by the addition of testicular extract containing among its enzymatic components the spreading factor of Duran-Reynals.

Methods and Materials:

Guinea pigs of both sexes (400-500 gm. body weight) were used; their rectal temperature being recorded daily. The antiorgan sera were prepared by immunization of rabbits with guinea pig spleen and bone marrow according to the original method of Marchuk (1943). Single 0.5 ml. subcutaneous injections of the serum diluted 1:5 in saline or in testicular extract (T.E.) were given using the abdominal area of the guinea pig.

*This study was aided by a grant from Lederle Laboratories Division, American Cyanamid Company. Department of Preventive Medicine and Public Health, The University of Texas Medical Branch, Galveston. Presented before the 48th general meeting of the Society of American Bacteriologists, Minneapolis, Minn., May 12, 1948.

The T. E. was made from freshly obtained guinea pig testes, following the technique of Zeckwer (1947). For this purpose ground testicular tissues were extracted in distilled water (volume equal to wet weight) and suspended in hypertonic saline followed by adjustment to isotonicity. After centrifugation (1500 rpm. for 15 min.) the supernatant was removed and used as diluent of the serum. A total of 0.5 ml. was injected into each test guinea pig about 15 min. prior to infection with epidemic typhus or spotted fever.† The presence of the "spreading factor" of Duran-Reynals in T. E. was evaluated in skin tests on normal guinea pigs using Evans blue as indicator.

Experiments and Results:

It was first investigated whether the addition of T. E. to a suspension of virulent rickettsiae would affect their invasiveness and influence the course of the disease. Previous findings by Duran-Reynals (1933) that *R. prowazeki* is devoid of the "spreading factor" added weight to this inquiry.

For this purpose a 10% suspension of brain in skim milk of a typhus guinea pig was uniformly mixed with an equal volume of T. E. (pH 7.2). Immediately afterwards the suspension was inoculated subcutaneously into 8 guinea pigs, 1 ml. each. Parallel controls were injected with the same brain suspension in saline, instead of T. E. As compared with the typical typhus fevers in all the controls, 3 animals of the T. E. series reacted with mild fevers after a protracted incubation, while 5 guinea pigs remained entirely afebrile. Judging from these preliminary experiments, the T. E. mixed *in vitro* with typhus rickettsiae seems to have had rather an inhibitory effect on the course of the disease. However, a similar experiment carried out with spotted fever resulted in a shortening of the incubation period and higher and more protracted fever reac-

†The strain of louse-borne typhus was secured through the courtesy of Dr. John P. Fox, Laboratories of the International Health Division, Rockefeller Foundation, New York. This strain was originally isolated by the U. S. Typhus Commission during the typhus epidemic in Naples, Italy. The Rocky Mountain spotted fever strain was kindly supplied by Dr. R. R. Parker, Director, Rocky Mountain Laboratory, U. S. Public Health Service.

tions of test guinea pigs as compared with the controls. These contrasting phenomena deserve further investigation.

The main part of this study was concerned with the possible effect of the T. E. on the action of the antiorgan serum in experimental typhus or spotted fevers *in vivo*.

The following is a representative experiment of the typhus series. Sixteen guinea pigs were inoculated subcutaneously with antiorgan immune rabbit serum (C. F. 1:1000; hemolysin titer 1:2560) diluted 1:5 in T. E. Dividing this series into 2 groups of 8 animals each, subcutaneous inoculation of typhus brain was given as follows: the first group was infected with typhus 2 inches distant from the serum entry site whereas the second group was infected at the site of serum entry. Eight guinea pigs remained afebrile during 18 days observation, 3 reacted with slight fever after 11 days incubation, 4 (2 in each group) manifested typical typhus fever and 1 died of pneumonia (Table I—condensed records). The recovered guinea pigs, including the afebrile ones, showed complete immunity when reinoculated with typhus one month after the initial infection.

Parallel to these series, 6 guinea pigs were treated with the same antiorgan serum diluted 1:5 in saline instead of T. E. Only 1 remained afebrile, another responded with slight fever, while 4 developed typical typhus.

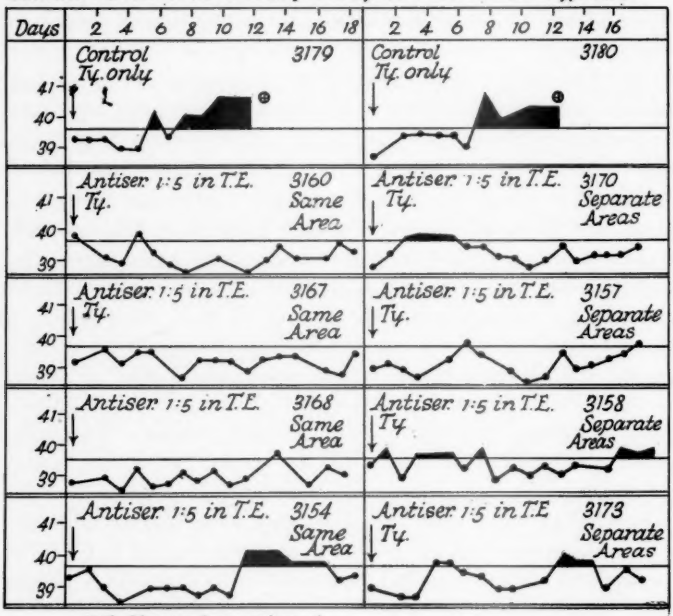
Normal sera obtained from rabbits before their immunization were used in control guinea pigs all of which developed typical typhus fever. This fact does not exclude the possibility that certain "normal" rabbit sera may modify the course of the infection as observed previously in dermal tests (Amigstein, Whitney and Beninson, 1948). Recent studies by C. M. Pomerat (unpublished) show (in tissue culture) a macrophage promoting factor present not only in the antiorgan sera but also in certain "normal" rabbit sera.

It seems, therefore, that the addition of T. E. to the system adds to the inhibition of typhus even when the infective inoculum is separated from the site of serum entry (Table I).

Similar experiments were carried out with the highly virulent Rocky Mountain spotted fever, where in addition to fever

TABLE I.

Fever charts of guinea pigs inoculated sbc. with Antiorgan Serum in T.E. and subsequently infected with Typhus.



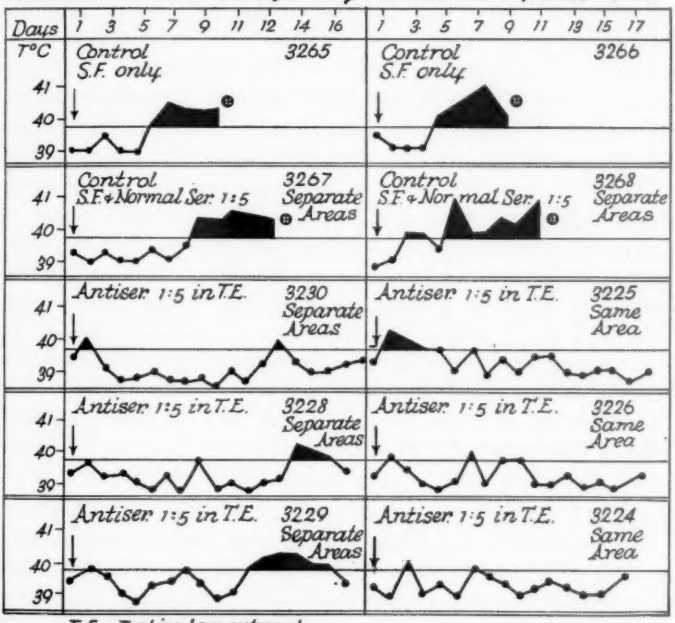
T.E. Testicular extract
⊕ Killed

the characteristic scrotal lesions and high fatality rate served as valuable criteria. A total of 34 test guinea pigs were divided into 2 groups: 16 were inoculated with antiorgan serum, and 18 with the same serum diluted in T. E. The combined results of the 2 groups infected with spotted fever showed during a 20 days observation 16 animals remaining afebrile, of which 10 were of the T. E. series and 6 treated with the antiserum alone. In addition, 2 of the latter group (serum alone) developed typical spotted fever. The remaining 16 guinea pigs showed abortive or moderate fevers, no scrotal lesions and complete recovery. On the contrary, the 18 controls treated with either T. E. alone or with normal rabbit serum in T. E. showed typical symptoms and a mortality rate of 80%. As in the typhus series, complete immunity to reinfection with spotted

fever was shown by the recovered and symptomless animals. As can be seen from the condensed records in Table II, inhibition of spotted fever resulted in both instances whether the inocula were given into separate or the same areas.

TABLE II

Fever charts of guinea pigs inoculated sbc. with Antiorgan Serum in T.E. and subsequently infected with Spotted Fever


Days
T°C
Control S.F. only 3265
Control S.F. only 3266
Control S.F.+Normal Ser. 1:5 3267 Separate Areas
Control S.F.+Normal Ser. 1:5 3268 Separate Areas
Antiser 1:5 in T.E. 3230 Separate Areas
Antiser 1:5 in T.E. 3225 Same Area
Antiser 1:5 in T.E. 3228 Separate Areas
Antiser 1:5 in T.E. 3226 Same Area
Antiser 1:5 in T.E. 3229 Separate Areas
Antiser 1:5 in T.E. 3224 Same Area

T.E. - Testicular extract
● - Killed

Summary and Discussion

As contrasted with our previous studies (Arngstein, Whitney and Beninson, 1948) when a single dermal area was the scene of interaction between serum and rickettsiae, the two-phase operation was divided in the present study into two distant areas.

Although the numerical significance of the results does not as yet justify definite conclusions, indications are that the pro-

tective action of the antiorgan serum is enhanced by the presence of testicular extract. This is particularly noticeable when the site of infection was separated by two inches from the serum inoculation site and could possibly be attributed to the testicular extract used as serum diluent. The synergistic action of hyaluronidase has lately been utilized clinically in the absorption of fluids given by hypodermoclysis (Hechter, Dopkeen and Yudell, 1947). It is therefore possible that the invasive enzymes in testicular extract may accelerate the diffusion of immune serum and stimulate the action of the latter on the connective tissues in localizing the infection. The suppressive character of the infection in the symptomless animals is corroborated by their ultimate immunity to reinoculation with typhus or spotted fever.

The rickettsiostatic effect of the antiserum used either alone or in conjunction with T. E. points to the protective action of the immune serum *per se*. It seems that the idea of stimulation of the connective tissues and their defensive forces by the low dosage of serum is gaining experimental support. As to the role of T. E. its invasive enzymes are presumably aiding the diffusion of the serum in the tissues in spite of the complex process of action and counteraction between the invasins and the defensive enzymes present in the sera of various animal species (Karl Meyer, 1947).

REFERENCES

Anigstein, L., Whitney, D. M., and Beninson, J.: Inhibition of typhus and spotted fever in guinea pigs by intradermal inoculation of antiorgan sera and of certain normal sera. Tex. Rep. Biol. and Med., 1948, *6*:87–96.

Duran-Reynals, F.: Studies on a certain spreading factor existing in bacteria and its significance for bacterial invasiveness. J. Exp. Med., 1933, *58*:161–181.

Hechter, O., Dopkeen, S. K., and Yudell, M. H.: The clinical use of hyaluronidase in hypodermoclysis. J. of Pediatrics, 1947, *30*:645–656.

Marchuk, P. D.: A method of preparing and preserving antireticular cytotoxic serum. Am. Rev. Sov. Med., 1943, *1*:113–123.

Meyer, K.: The biological significance of hyaluronic acid and hyaluronidase. Physiol. Rev., 1947, *27*:335–359.

Pomerat, C. M.: (unpublished data).

Zeckwer, I. T.: Limitation of spreading factor in injured rats. Arch. of Path., 1947, *44*:356.

AN EFFECTIVE ANTIVIRAL SYNTHETIC*

MURRAY SANDERS, Y. SUBBAROW AND R. C. ALEXANDER†

Specific therapeutic agents against true animal or human viruses have not heretofore been available. Although recent reports indicate that therapy against the members of the lymphogranuloma-psittacosis group is a likelihood in the near future, it is generally agreed that such viruses as trachoma, inclusion blennorrhea, psittacosis, lymphogranuloma venereum and meningopneumonitis are more closely related to the rickettsiae than to such agents as herpes simplex, equine encephalomyelitis, poliomyelitis, etc.

The present communication is a general statement of the successful use of a chemotherapeutic agent against a mouse virus. Detailed data on numerous experiments involving thousands of mice and more than a hundred monkeys will be published at a later date.

In 1947 a large number of compounds were tested at the Lederle Laboratories for possible activity against an experimentally induced infection with a strain of western equine encephalomyelitis virus. The activity of these compounds was determined by treating mice infected at least 48 hours prior to receiving drug treatment. Among these compounds a new sulfonamide synthesized at the Calco Chemical Division of the American Cyanamid Company showed promise. The compound, N-(2-thiazolyl)-phenol sulfonamide, was named pheno-

*The phases of this investigation which involved mice and tissue cultures were aided by a research grant (RG 558) from the United States Public Health Service. Monkey experiments were made possible by a grant from the Lederle Laboratories.

†From the Departments of Bacteriology and Ophthalmology, College of Physicians and Surgeons, Columbia University, New York, and the Lederle Laboratories, Division of American Cyanamid Company, Pearl River, New York. Received for publication June 15, 1948.

sulfazole.[1] In September, 1947, permission was received to test this drug against poliomyelitis.[2]

The Test Virus

The strain of virus selected as the infection to be treated was a mouse virus originally isolated in 1940. It was used throughout the present study for the following reasons:

1. It is infectious for mice in high dilutions by all routes of inoculation.
2. It is a stable and predictable virus, producing encephalitis and paralysis in mice.
3. It can be grown in tissue culture with ease and in this milieu produces an infection in mice predominantly paralytic in character.

In order to obtain a fairly standardized seed virus, the supernate of a fluid tissue culture was injected intracerebrally into 200 Swiss mice weighing approximately 10 to 12 grams. As symptoms of encephalitis and paralysis appeared, the brains of 72 moribund animals were pooled. After emulsification in a Waring blender the mouse brain pool, diluted by weight to 20% with a mixture of 10% horse serum in Simms salt solution, was distributed in vials and stored in CO_2 ice. During the past 9 months, this pool has consistently yielded titers of approximately 10^{-7} in mice infected via the intraperitoneal route.

The Drug

Phenosulfazole, N-(2-thiazolyl)-phenol sulfonamide, is a white powder that goes into solution with difficulty. Since it became apparent in the early experiments that the powder was not efficiently absorbed, a sodium salt of the drug was made. This salt has proved to be soluble, non-toxic and generally satisfactory as an injectable material. The results in mice

---

[1]Trade name Darvisul.

[2]We wish to express our deepest appreciation to Mr. Fritz Popken and his associates for placing their data at our disposal prior to publication and to Dr. M. E. Hultquist and his associates for making available a supply of the drug.

summarized in Table I have been obtained with the use of the sodium salt.

Schedule and Course of Treatment in Mice

Various schedules of treatment were investigated in the early experiments. For present purposes, it is sufficient to say that the schedule now used in this laboratory is as follows:

Swiss mice weighing 16 to 20 grams are injected intraperitoneally with 0.06 ml. serial dilutions of the mouse brain pool. The groups of mice receiving the range of dilutions of virus within which it is desired to attempt treatment (usually $2x10^{-4}$, $2x10^{-5}$, $2x10^{-6}$, $2x10^{-7}$) receive the first injection of drug 24 hours after the intraperitoneal injection has been given. Once treatment has been initiated, each mouse receives 4 daily injections, at 8 A.M., 12 NOON, 3 P.M., and 6 P.M.

At 8 A.M. 0.5 ml. of drug is given and at 12 NOON and 3 P.M. the dose is 0.25 ml. At 6 P.M. 1.0 ml. of drug is injected. Thus each animal receives a total daily fluid injection of 2.0 ml. Since the concentration of drug has been either 4 or 8 mgms. per ml., the daily intake of drug per animal is either 8 or 16 mgms. This schedule is maintained for five days.

In a recent experiment involving 300 mice the treatment schedule was altered so that a daily total of 16 mgms. of drug was given in two injections, one ml. containing 8 mgms. at 8 A.M. and another at 6 P.M. The results suggest that this schedule is at least as effective as a course of treatment given four times daily (Exp. F, Table I).

It is to be emphasized that large mice (at least 16 to 20 grams) have been found to be better experimental subjects. Indeed the slight irregularities noted in Experiments A, B and C (Table I) were found to be due to smaller mice. When animals weighing less than 15 grams were eliminated from the experiment, the results were more consistent (Exp. D, Table I).

It should also be noted that treatment was initiated 24 hours after infection for the following reason: In the original studies with this agent it was found that the virus was unusually invasive once it was placed in the peritoneal cavity. Indeed, within 2 hours after intraperitoneal injection, the virus could

TABLE I

ACTIVITY OF SODIUM PHENOSULFAZOLE

A summary of experiments in which treatment was started 24 hours after a pool of mouse poliomyelitis virus was inoculated intraperitoneally into the mice. Results on Fifth and Fourteenth Days after Infection

Experiment	Results on	Total Dose of Drug in Milligrams	SURVIVORS/TOTAL in Dilutions of Virus Tested				% Survivors (14 Days)	Final Titer (14 Days)
			10^{-4}	10^{-5}	10^{-6}	10^{-7}		
A	5th Day	35	15/20	19/20	14/20	18/20		
	14th		6/20	17/20	11/20	17/20	63	$10^{-4.8}$
	5th Day	0 (controls)*	0/20	2/20	0/20	14/20		
	14th		0/20	0/20	0/20	12/20	15	$10^{-6.8}$
B	5th Day	80	16/18	8/18	10/18	18/18		
	14th		9/18	7/18	8/18	14/18	52	$10^{-5.5}$
	5th Day	40	14/18	12/18	14/18	12/18		
	14th		8/18	7/18	10/18	11/18	50	$10^{-5.7}$
	5th Day	0 (controls)	0/18	0/18	3/18	10/18		
	14th		0/18	0/18	0/18	8/18	11	$10^{-7.0}$
C	5th Day	40	6/10	7/10	6/10	8/10		
	14th		4/10	6/10	5/10	8/10	57	$10^{-5.1}$
	5th Day	0 (controls)	0/10	0/10	3/10	4/10		
	14th		0/10	0/10	0/10	4/10	10	$10^{-7.0}$

*Control animals received intraperitoneal injections of 0.85% saline comparable in regard to volume of fluid and schedule with mice under treatment. Additional controls consisted of animals receiving serial dilutions of virus in the usual fashion (i.e., without saline injections). No significant differences were observed in the two types of controls. At all times, the number of animals was the same in the control groups as in the treated groups.

†In this experiment selected mice weighing 16 to 20 grams were used.

‡Two doses of drug daily for 5 days (8 mgms. in 1.0 ml. at 8 a.m. and another at 6 p.m.).

TABLE I (Continued)

Experiment	Results on	Total Dose of Drug in Milligrams	SURVIVORS/TOTAL in Dilutions of Virus Tested				% Survivors (14 Days)	Final Titer (14 Days)
			10^{-4}	10^{-5}	10^{-6}	10^{-7}		
D†	5th Day	80	10/15	14/15	12/15	13/15		
	14th		7/15	8/15	12/15	10/15	61	$10^{-5.0}$
	5th Day	40	8/15	11/15	11/15	14/15		
	14th		2/15	8/15	11/15	10/15	51	$10^{-5.4}$
	5th Day	0 (controls)	0/15	0/15	2/15	5/15		
	14th		0/15	0/15	0/15	5/15	8	$10^{-7.0}$
E†	5th Day	80	4/15	7/15	12/15	12/15		
	14th		3/15	6/15	11/15	12/15	53	$10^{-5.8}$
	5th Day	0 (controls)	0/15	0/15	1/15	7/15		
	14th		0/15	0/15	0/15	5/15	8	$10^{-7.0}$
F‡	5th Day	80	5/10	8/10	10/10	10/10		
	14th		5/10	7/10	9/10	9/10	75	$10^{-4.8}$
	5th Day	0 (controls)	0/10	0/10	2/10	5/10		
	14th		0/10	0/10	0/10	4/10	10	$10^{-7.0}$

*Control animals received intraperitoneal injections of 0.85% saline comparable in regard to volume of fluid and schedule with mice under treatment. Additional controls consisted of animals receiving serial dilutions of virus in the usual fashion (i.e., without saline injections). No significant differences were observed in the two types of controls. At all times, the number of animals was the same in the control groups as in the treated groups.

†In this experiment selected mice weighing 16 to 20 grams were used.

‡Two doses of drug daily for 5 days (8 mgms. in 1.0 ml. at 8 a.m. and another at 6 p.m.).

be demonstrated in all the tissues of the mouse. It seemed, therefore, that any therapeutic results obtained after a 24-hour infection period would be significant.

A summary of several experiments carried out under the experimental conditions stated above is given in Table I.

It is apparent from Table I that sodium phenosulfazole is effective against as many as 100 LD_{50}'s of the mouse poliomyelitis strain used in this study. It is of interest to note that no control mice survived in dilutions below $2x10^{-7}$, and since the lethality of this mouse strain has been frequently observed in this and other laboratories, the presence of survivors in the treated groups is of particular significance.

On the basis of these and other experiments, a strong impression has been received that with slight changes in the treatment schedule and careful selection of mice (18 to 20 grams) the compound under discussion is consistently effective against *at least* 100 intraperitoneal LD_{50}'s of SK mouse poliomyelitis.

Prophylactic Feeding

On two occasions sodium phenosulfazole has been given in 4 mgm. amounts to mice by gavage. Six to seven hours after the drug was placed in the stomach of the animals, they were injected intraperitoneally with 0.06 ml. of a 10^{-6} dilution of mouse brain pool. In the first experiment, 25 of 45 mice survived and in the second, 18 of 34 animals survived. In both experiments no control mouse survived the 10^{-6} assault dose of virus.

The survivors of the drug-treated animals were immune to a second dose of virus (10^{-6}) given intraperitoneally 3 weeks after the first dose.

This finding is considered one of the most important of the current study and is being investigated further with large numbers of animals.

In monkeys, drug dosage has ranged from 250 mgms. to 400 mgms. per kg. body weight. The results of these therapeutic studies will be published at a later date. For present purposes it is sufficient to note that the monkey schedule has been extended for as long as 10 days without apparent ill effect. On

one occasion post-mortems on 11 monkeys which had received 400 mgms. per kg. body weight for 10 days revealed, grossly, a complete lack of pathology.

On the other hand, it should be noted that our observations have been limited to mice and monkeys. If other species of animals are exposed to this drug, it will be necessary to determine the range of tolerance for each species. That sodium phenosulfazole is a powerful tissue reactor is apparent from our tissue culture experiments and from the reaction of one monkey studied for acute toxicity. This animal received a total of 1.0 gm. per kg. of a 25% suspension of drug administered intravenously during a 30-minute interval. Within 60 minutes following the injections the monkey showed signs of cortical stimulation, had convulsions and died. In contrast to this experience, a group of 3 monkeys received 2.0 gms. per kg. body weight over a period of 3 days and showed no ill effects.

Immunity in Treated Mice

It is worthy of note that evidence is available showing that mice infected with SK mouse poliomyelitis and successfully treated with sodium phenosulfazole are immune to reinfection with the same virus.

Monkey Experiments

The effect of sodium phenosulfazole is being studied in macacus rhesus monkeys infected by the intracerebral route with a human strain of poliomyelitis. This work is being extended to include various species of monkeys and routes of infection and will be reported in detail at a later date.

Tissue Culture Experiments

When in the early phases of this study phenosulfazole showed promise of exerting an antiviral effect in infected mice, it became of interest to determine whether the drug was acting directly on the virus or on the cellular substrate. Fluid tissue cultures were selected for this phase of the investigation since the mouse virus had been comprehensively studied *in vitro* and data were available for normal growth and deterioration curves.

The fluid cultures of serum ultrafiltrate and embryonic mouse brain were prepared in the same manner as previously described. To date, thirteen major experiments have been carried out with fluid cultures and phenosulfazole, and a detailed description will be included in a more comprehensive report. At this time it is desired to give a brief statement of our experiences emphasizing the factors which appear to be important in this type of work. The experiment summarized in Table II has been selected as representative.

When the virus was placed in a cell-free serum ultrafiltrate medium, the disappearance of the infectious agent followed the normal deterioration curve. Since it was soon apparent that phenosulfazole did not act directly on the virus, the drug was placed in infected embryonic mouse brain cultures to see what the effect would be on the virus growth curve. As may be seen in Table II, the inhibition of virus propagation was abrupt; the routine infected tissue culture having a mouse intracerebral titer of $10^{-5.5}$ and a parallel or sister culture to which 10 mgms. of phenosulfazole had been added having a titer of $10^{-1.0}$. This effect has been consistently obtained.

Because phenosulfazole is a sulfonamide, it was obviously desirable to see whether a parabenzoic compound would have an antagonistic effect on it. Accordingly, parahydroxybenzoic acid in 10 mgm. amounts was added to the culture-virus-phenosulfazole system. It is of interest that the antagonistic

TABLE II

The Effect of Phenosulfazole and Parahydroxybenzoic Acid on Virus Infected Tissue Cultures

Culture	Days incubated before titration in mice	Mouse Titer (intracerebral inoculation)
A. Forty-first serial passage of mouse virus in serum ultrafiltrate, embryonic mouse brain fluid cultures.	3	$10^{-5.5}$
B. 10 mgms. of Phenosulfazole added to Culture "A" (at time Culture "A" was titrated).	3	$10^{-1.3}$
C. 10 mgms. of Parahydroxybenzoic Acid added to Culture "B" (at time Culture "B" was titrated).	2 3 4	$10^{-2.5}$ $10^{-3.0}$ $10^{-3.3}$

effect was easily demonstrable. In the very same tissue culture (the one containing phenosulfazole in which the titer was $10^{-1.0}$) the addition of the parahydroxybenzoic acid produced an increase in titer of $10^{-3.3}$ in 96 hours.

The question may well be raised why the final virus potency, following manipulation of the culture with the drug and its antagonist, was lower than the original culture, *i.e.*, $10^{-3.3}$ as against $10^{-5.5}$. It must be remembered that the embryonic mouse brain cells which constitute the cellular elements of the fluid culture are, under optimal circumstances, in a quiescent or resting phase rather than in a proliferative phase. Such cells are susceptible to environmental changes and deteriorate rapidly. One of the most likely sources of trauma is the addition of the parahydroxybenzoic acid. It is apparent from the indicator present in the serum ultrafiltrate medium that an extreme change in pH takes place unless the chemical is added carefully.

Furthermore, the effect of ageing on the culture cannot be overlooked. By the time the parahydroxybenzoic acid phase of the experiment is tested 9 days have elapsed; 3 days for the routine growth of the virus in a freshly made culture; 3 days for the phenosulfazole, or inhibition phase; and 3 days for the neutralization phase of parahydroxybenzoic acid. If 9-day points are checked on the growth curve for this virus, it will be seen that $10^{-3.0}$ is an average value for routinely infected cultures. This fact was, of course, also checked with routine control cultures. It may be stated that the antagonistic action of parahydroxybenzoic acid is a complete one and that the lower final titers suggest a minimum of tissue damage. These observations are stressed because the phenosulfazole-parahydroxybenzoic acid reaction appears to be a promising instrument for the study of cell-virus relationships.

The various steps of the tissue cultures have occasionally been checked in plasma drop preparations to see what cellular damage occurred as the result of exposure of the tissues to the drug and its antagonist. It has been difficult to evaluate such preparations since normal embryonic mouse brain tissue removed from fluid tissue cultures to plasma cultures in Carrel flasks do not show much capacity for proliferation, although such cells still support virus growth. The correlation between

plasma preparations and fluid virus cultures is very important. This phase of the investigation is being studied.

Toxicity

One of the most striking aspects of the current study has been the apparent lack of toxicity of sodium phenosulfazole for mice and monkeys. Detailed data on the work done at the Lederle Laboratories and at Columbia University will be published in the near future. In our hands, the principle of non-toxicity was confirmed since it was not unusual to have large numbers of mice receive 1.0 gram of drug per kg. body weight for five days (Exps. B, D, Table I) for a total intraperitoneal dosage of 5.0 grams per kg. At no time were ill effects noted in these animals which were frequently observed for 21 days and longer. Numbers of these animals have been completely autopsied for microscopic studies, and there is evidence for believing that the gross impression is confirmed by tissue sections.

Conclusions

1. Sodium phenosulfazole (Darvisul), N-(2-thiazolyl)-phenol sulfonamide, is effective against as many as 100 LD_{50}'s of a mouse poliomyelitis virus when intraperitoneal treatment is instituted 24 hours after intraperitoneal infection.
2. The efficacy of this drug depends upon a proper dosage and time schedule.
3. The size of the mouse (16 to 20 grams) is important in carrying out the therapeutic studies.
4. Mice receiving treatment and surviving an initial infection are relatively immune to reinfection.
5. In two experiments more than half of the mice receiving a single dose of sodium phenosulfazole by mouth were resistant to a 10^{-6} virus challenge which killed all control animals. The survivors were immune.
6. Phenosulfazole in serum ultrafiltrate tissue cultures does not act directly on the mouse virus but appears to derive its antiviral properties by reacting with the cellular substrate.
7. Parahydroxybenzoic acid nullifies the antiviral effect of phenosulfazole in tissue cultures.

8. Sodium phenosulfazole has been strikingly non-toxic in the two experimental hosts studied, mice and monkeys.
9. The effect of sodium phenosulfazole is being studied in monkeys infected with a human strain of poliomyelitis.

REFERENCES

Smadel, J. E., and Jackson, E. B.: *Science*, October, 1947, *106*:418.
Wright, L. T., Sanders, M., Logan, M., Priggot, A., and Hill, L.: *J.A.M.A.*, in press.
Popkin, F. et al: to be published.
Hultquist, M. E. et al.: to be published.
Jungeblut, C. W., and Sanders, M.: *J. Exper. Med.*, 1940, *72*:407.
Sanders, M., and Jungeblut, C. W.: *J. Exper. Med.*, 1942, *75*:631.
Simms, H. S., and Sanders, M.: *Arch. Path.*, 1942, *33*:619.
Cunningham, R.: to be published.
Wolf, A., Cowen, D., and Sanders, M.: to be published.
Reed, L. J., and Muench, H.: *Am. J. Hyg.*, 1938, *27*:493.

* * * * * * * * * * *

NOTE: Since receipt of this report, Doctor SubbaRow died suddenly of coronary disease. His death deprives his colleagues of a vigorous and inspiring associate.

Yellapragada SubbaRow was born in 1896 in Madras, where he received his collegiate training. As a Rockefeller Foundation Fellow, he obtained his doctoral degree from Harvard, where later he was associate professor of biochemistry. Since 1942 he has been Director of Research of the Lederle Laboratories. His chief interests were in phosphorus metabolism, liver factors, antibiotics, and bacterial nutrition.

CALLING ATTENTION TO:

Items of Possible Interest to Friends of Our Effort
June, 1948

1. Books Again: Galveston orchids (oleanders) to M. Fishbein and National Foundation for Infantile Paralysis for promoting fine editorial job of R. Dubos: *Bacterial and Mycotic Infections of Man*, and T. Rivers: *Viral and Rickettsial Infections of Man* (Lippincott, Phila., 1948, 750 pp., and 544 pp., $10 set). Helpful is *Symposium on Mediocolegal Problems* (Lippincott, Phila., 1948, 250 pp., $5). A Szent-Gyorgyi blurbs on *Nature of Life: A Study of Muscle* (Academic Press, NY10, 1948, 94 pp., $3). On the band-wagon climbs a symposium on *Sex Habits of American Men* (Prentice-Hall, N.Y., 1948, $3). H. G. Wolff offers important *Headache and Other Head Pain* (Oxford Press, N.Y., 1948, 664 pp., $12). O. Rahn describes *Injury and Death of Bacteria by Chemical Agents* (Biodynamica, Normandy, Mo., 1948, 185 pp., $4). S. R. Kagan edits *Victor Robinson Memorial Volume: Essays on History of Medicine* (Froben, N.Y., 1948, 447 pp., $10). E. Moschcowitz analyses *Biology of Disease* (Grune and Stratton, N.Y., 1948, 228 pp., $4.50). T. Addis well discusses *Glomerular Nephritis* (Macmillan, N.Y., 1948, 338 pp., $8). W. C. Menninger in *Psychiatry in a Troubled World* brilliantly analyses history of psychiatry in U. S. Army in World War II and applies observations to civilian practice (Macmillan, N. Y., 1948, 650 pp., $6). A. E. Cohn brings some essays together in *No Retreat from Reason* (Harcourt, Brace, N. Y., 1948, 288 pp., $3.50). A wise approach to scientific ethics is offered by S. J. Holmes in *Life and Morals* (Macmillan, N.Y., 1948, 242 pp., $3). Wisely inspiring is D. E. Cameron in *Life is for Living* (Macmillan, 1948, 247 pp., $2.70). L. S. Stebbing discusses *Ideals and Illusions*, (Watts, London, 1948, 80 pp., 3s 6d). E. Huntingdon investigates *Mainsprings of Civilization* (Chapman, Hall, London, 1948, 660 pp., 29s). T. N. Norris describes *Dehydration of Food* (Chapman, Hall, London, 1948, 184 pp., 15s). R. T. Williams edits Biochemical Soc. Symposium No. 1: *Relation of Optical Form to Biological Activity in Amino Acids* (Cambridge Univ. Press, 1948, 120 pp., 5s). A. Smith (AMA) revives useful *Technic of Medication* (Lippincott, Phila., 1948, 300 pp., $3). R. H. Follis describes *The Pathology of Nutritional Disease* (C. C. Thomas, Springfield, Ill., 1948, 302 pp., $6.75). W. F. Peterson enjoys *Man, Weather and Sun* (C. C. Thomas, Springfield, Ill., 1948, 493 pp., $10).

2. Enzymes: G. T. and C. F. Cori do some neat enzyme crystallizing (*J. Biol. Chem.* 173/591/48). A. M. Robinson and F. L. Warren find acid phosphatase inhibitors in urine (*Nature* 161/397/Mch. 13/48). G. H. Bourne notes alkaline phosphate in taste buds and nasal mucosa (*Ibid.* 445/March 29). J. H. Milstone offers 3 stage analysis of blood coagulation

emphasizing enzyme systems and calcium (J. Gen. Physiol. 31/301/48). S. E. Lewis reports methyl bromide inhibits SH enzymes (*Nature* 161/692, May 1, 1948). W. E. Knox and Co., explain bactericidal action of chlorine on basis of inhibition of SH enzymes (*J. Bact.*, 55/451, 1948). M. Calvin and A. A. Benson trace path of carbon in photosynthesis (*Science*, 107:476, May 7, 1948). P. Ohlmeyer finds fluoride inhibition of phosphatase reversed by magnesium salts (*Hoppe-Seyler's Ztschr. Physiol. Chem.*, 282/1, 1945—revived by A. Butenandt and K. Thomas, Bd. 282, Heft 1 and 2, January, 1945; Heft 3 and 4, July, 1947).

3. Blood: J. Bichel says p-amino benzoic acid causes increased leucocyte count in leukemia but not in health (*Nature*, 161:353, March 6, 1948). E. L. Smith purifies liver anti-pernicious anemia factor free from folic acid (*Ibid.*, 638, April 24, 1948) agreeing with E. L. Rickes & Co., who crystallize it as vitamin B_{12} (*Science*, 107:396, April 16, 1948). W. Ashby discusses life span of RBC and indicates endocrine influence (*Blood*, 3:486, 1948). T. H. Ham study thermal injury to RBC (*Ibid.*, 373; issue dedicated to G. R. Minot). O. Olbrich continues studies on blood changes in aged (*Edin. Med. Surg. J.*, 55:100, 1948 . J. E. Markee reviews morphological basis for menstrual bleeding (*Bull. N.Y. Acad. Med.*, 24:253, 1948). D. V. Davies and D. A. W. Edwards describe blood supply of synovial membrane (*Ann. Roy. Col. Surg. Eng.*, 2:142, 1948).

4. General: H. Hyden and H. Hartelius report stimulation of nucleoprotein production by malononitrile with beneficial effect in mental disorder (*Acta. Psych. Neurol.*, Suppl. XLVIII, Copenhagen, 1948). F. Heinmann concludes lipids are not antigenic by virtue of combination with foreign protein (*Schw. Ztsch. Path. Bact.*, 11:1, 1948). J. R. Moreton shows importance of physical state or lipids causing atherosclerosis (*Science*, 107:371, April 9, 1948). Royal Society sponsors important scientific information conference in London June 21–July 2, 1948. H. N. Munro and M. C. Cumming (*Nature*, 161:560, April 10, 1948) confirm D. P. Cuthbertson (*Quart. J. Exp. Physiol.*, 29:13, 1939) that nitrogen loss after fracture comes from sources other than injured part. A. A. Abbie offers philosophical discussion of individual and environment (*Med. J. Austral.*, 1:321, March 13, 1948). A Faller gives fine historical account of anatomical preparations from Galen to present (*Acta. Anatom.* Suppl. VII, Karger, Basle, 1948, 115 pp). E. de Robertis and F. O. Schmitt find neurotubules in axis cylinder of nerve fibers with repeating pattern of cross bands (*J. Cell. Comp. Physiol.*, 31:1, 1948). Many fine articles in T. Addis Festschrift (*Stanford Med. Bull.*, 6:3–275, 1948). F. A. Jones pertinently comment on full-time specialist (*Lancet.*, 1:433, March 20, 1948). J. H. Sheldon emphasizes direct observation in studying old age (*Ibid.*, 621, April 24, 1948). Our J. McGivney discusses healing of anorectal surgical wounds (*South. Med. J.*, 41:401, 1948).

JULY, 1948

1. PHARMACOLOGICAL: L. E. Craig reviews curariform activity and chemical structure (*Chem. Rev.*, 42/285/48). E. Baldwin reports neat screening job on anthelmintics, confirming value of phenolic carbamates (*Brit. J. Pharmacol. Chemoth.*, 3/93/48). D. G. Evans and others find that adrenaline injections enhance bacterial infections (*Brit. J. Exper. Path.*, 29/20/48). P. A. A. Weterings confirms inhibition of respiration by increased oxygen pressure in blood plasma (*Acta Med. Scand.*, 130/232/48). L. Goldberg recommends sorbide dinitrate as long acting non-toxic vaso-dilator (*Acta Physiol. Scand.*, 15/173/48). W. K. Noell recommends that post resuscitation treatment from severe anoxia be based on that for cerebral concussion, rather than use analeptic drugs which are helpful chiefly in acute narcotic poisoning (*Air Univ. School Aviation Med. Proj. 519, Rep. 1*, Randolph Field, '48,—why not set up a journal?). L. Oliski describes resistance-lowering effect of mucin (*Bact. Rev.*, 12/149/48). J. J. Reuse finds neoantergan most specific antihistaminic (*Brit. J. Pharmacol. Chemoth.*, 3/174/48). J. Wolff and I. L. Chaikoff demonstrate how plasma inorganic iodide regulates thyroid function (*J. Biol. Chem.*, 174/555/48). O. Bodansky shows inhibitory effect of amino acids on phosphatase (*ibid.*, p. 465). H. N. Glassman reviews surface acting agents and applications (*Bact. Rev.*, 12/105/48). M. A. Jamra and F. T. Mendes report value of urethane in treating myeloid and chronic lymphatic leukemia (Revis. Hosp. Clin., 3/23/48). M. F. Guyer and P. E. Claus report lung tumor after IP injections of urethane (*Cancer Res.*, 7/342/48). Our R. H. Rigdon recommends blood transfusion and oxygen as supportive therapy in malaria (*Am. J. Clin. Path.*, 18/485/48). S. Farber uses aminopterin in leukemia (*New Eng. J. Med.*, June 3/48). J. J. Gordon and J. H. Quastel note effects of organic aresenicals on enzymes systems, suggesting mapharsen for detection of thiol enzymes (*Biochem. J.*, 42/337/48). G. A. Levvy and others report that hepato and nephro toxic agents increase glucuronidase activity (*ibid.*, p. 462). K. von Dongen and others review sparteine and observe antagonism to acetylcholine (*Arch. Internat. Pharmaco.*, 76/163/48). Excellent review on chemotherapy of filariasis, including Y. SubbaRow, R. I. Hewitt, and B. K. Harned on the alkyl piperazine, "Hetrazan," which looks so promising clinically (*Ann. N.Y. Acad. Sci.*, 50/19–170/48).

2. CLINICAL: R. F. Vaccarezza, C. J. Nunez, N. N. Stapler, F. G. Capurra and others sympose on intestinal TB (*Revis. Asso. Med. Argentina*, 62/175/214/Apr. 15/48). A. Wallgren and H. Malmros after critical analysis, recommend BCG vaccination vs. TB (*Brit. Med. J.*, 1/1126–1132/June 12/48). J. and T. Gillman discuss liver and anoxia with reference to shock and malnutrition (*S. Afr. J. Med. Sci.*, 13/11/48). E. A. Sellers, C. C. Lucas and C. H. Best analyse lipotropic factors in cirrhosis (*Brit. Med. J.*, 1/1061/June 5/48). B. A. Houssay reviews experimental diabetes (*J. Physiol.*, 39/249/48). H. Jesserer and A. Pillat suggest subcutaneous bone implant for handling chronic calcium deficiency tetany

(*Wien Klin. Wchnschr.*, 60/302/May 14/48). G. H. Monrad-Krohn notes neurologic and emotional factors in prosodic qualities of speech (*Acta Psych. Neurol.*, 22/255/48). M. L. Peterman and K. R. Hogness reveal by electrophoresis a peculiar acid protein in plasma of gastric cancer patients (*Cancer*, 1/104/48). Note symposium on hemorrhage (*Ann. N.Y. Acad. Sci.*, 49/483–660/48). M. A. B. Brazier shows EEG changes caused by oxygen lack or low sugar occur in same neuronal population (*J. Neurol, Neurosurg. Psych.*, 11/118/48). L. J. Bellamy and C. H. Watt note sulfur factors in deactivation of penicillin solutions by rubber tubing (*Nature*, 161/940/June 12/48). F. J. Laranja and others note high incidence of right bundle branch block in Chagas disease (*Brasil Med.*, 62/51/48).

3. AMUSICAL: J. Sacks reviews radiactive isotopes as bioindicators (*Chem. Rev.*, 42/411/48). Our C. N. Frazier and H. C. Li report *Racial Variations in Immunity to Syphilis* (Univ. Chicago Press, '48, 130 pp., $2.50). H. G. Wolff bulls-eyes with *Headache and Other Head Pain* (Oxford Press, N.Y. 11, '48, 664 pp., $12). Helpful is *Symposium on Medicolegal Problems* (Lippincott, Phila., '48, 255 pp., $5). F. D. Mott and M. I. Roemer study *Rural Health and Medical Care* (McGraw Hill, N.Y., '48, 610 pp., $6.50). Stimulating is *Widening Horizons in Medical Education: A Study of the Teaching of Social and Environmental Factors in Medicine* (Commonwealth Fund, N.Y., '48, 242 pp., $2.75). R. Barer discusses structure of striated muscle fiber (*Biol. Rev. Cambridge Philo. Soc.*, 23/159/48). A. L. Nielsen in studying mechanisms of glycusuria finds upper limit of usual glucose renal reabsorption to be 300 mgm/min (*Acta Med. Scand.*, 130/219/48). S. Haberman and J. M. Hill demonstrate anti-D agglutinin and antigen (*Blood*, 3/682/48) predicted by R. A. Fisher and R. R. Race (*Nature*, 153/771/44). G. E. Burch finds 34.4°C. and 50% humidity the threshold levels for sweating in healthy adults resting in bed (*Proc. Soc. Exper. Biol. Med.*, 67/521/48). D. Pressman and G. Keighley show by radiactive iodine that zone of activity of antikidney serum is kidney only (*J. Immunol.*, 59/141/48). Be sure to read E. U. Condon's discussion of Science and Security (*Science*, 107/659/June 25/48).

AUGUST, 1948

1. LOTS OF NEW BOOKS: Important is symposium on *The Use of Isotopes in Biology and Medicine*, by 19 distinguished contributors (Univ. Wisconsin Press, Madison, '48, 460 pp., $5). Ditto is *Approaches to Tumor Chemotherapy* (A.A.A.S., Washington, '48, 450 pp., $7.75). Practical is H. A. Christian's *Bright's Disease* (Oxford Univ. Press, N.Y., '48, 400 pp., $9). P. M. Aggeler and S. P. Lucia discuss *Hemorrhagic Disorders* (Univ. Chicago Press, '48, 112 pp., $10). C. N. Frazier and Li Hung-Chiung report on *Racial Variations in Immunity to Syphilis* (Univ. Chicago Press, '48, 128 pp., $2.50). L. Van den Berghe and A. Dubois describe *Diseases of Warm Climates* (Grune & Stratton, N.Y., '48, 450 pp., $8.75). E. Ponder offers *Hemolysis and Related Phenomena* (Grune & Stratton, N.Y., '48,

300 pp., $6). J. M. Hill and W. Dameshek edit *The Rh Factor in Clinic and Laboratory* (Grune and Stratton, N.Y., '48, 200 pp., $4.25). W. Dameshek and Estren discuss *The Spleen and Hypersplenism* (Grune and Stratton, N.Y., '48, 180 pp., $4.75). P. H. Hoch confesses *Failures in Psychiatric Treatment* (Grune & Stratton, N.Y., '48, 320 pp., $4.50). R. R. MacIntosh and W. W. Mushin do fine job in *Physics for the Anesthetist* (C. C. Thomas, Springfield, Ill., '48, 235 pp., $7.50). E. M. Brockbank offers useful *Conduct of Life Assurance Examinations* (Lewis, London, '48, 176 pp., 12s 6d). R. Lee and W. A. Hanson offer *Protomorphology: The Principles of Cell Auto-Regulation* (Lee Foundation, Milwaukee, '48, 365 pp., free and worth it). N. C. Foot helps in *Identification of Tumors* (Lippincott, Phila., '48, 420 pp., $6). H. F. Dowling discusses *Acute Bacterial Diseases* (Saunders, Phila., '48, 465 pp., $6.50). E. E. Ledbetter suggests *Peace by Thinking* (Bloch, Chicago, '48, 486 pp., $3.50). H. E. J. Houssay offers excellent monograph on *Hipofisis y Crecimiento* (Ateneo., Buenos Aires, '48, 293 pp., $6). J. A. Myers and C. A. McKinlay edit *The Chest and the Heart* (C. C. Thomas, Springfield, Ill., '48, 2 vols., 1800 pp., $25).

2. Physiological: E. Grandjean reviews altitude physiology (*J. Physiologie*, 49/51A/48). A. Jost reviews humoral control of sex differentiation (*Biol. Rev. Cambridge Philosoph. Soc.*, 23/201/48). B. Chance describes enzyme substrate compounds of catalase and peroxides (*Nature*, 161/915/June 12/48). G. Reid finds muscle stimulating substance in serum and platelets which directly stimulates adrenal medulla (*Austral. J. Exper. Biol. Med. Sci.*, 26/107/48). G. Fraenkel describes vitamin B_t in relation to pterins and other anti-anemic factors (*Nature*, 161/981/June 19/48). A. J. Sica and others find pteroyl glutamic acid and xanthopterin helpful for lactation (*Arch. Biochem.*, 18/119/48). G. W. Harris reviews neural control of the pituitary gland (*Physiol. Rev.*, 28/139/48). P. R. Cannon surveys tissue protein synthesis (*Fed. Proc.*, 7/391/48). R. F. Pitts reviews renal excretion of acid (*ibid.*, p. 418). I. Spadolini describes excitatory and inhibitory action of acetylcholine and adrenin as function of concentration at autonomic effectors (*Arch. Internat. Physiol.*, 55/317/48). Our H. G. Swann's memo report 696-79G U.S. Air Force, Wright Field, Dayton, "Studies in Resuscitation" deserves more satisfactory publication. E. Gellhorn and H. Safford study autonomic balance in anoxia, electro and insulin shock (*Proc. Soc. Exper. Biol. Med.*, 68/74/48).

3. Clinical Microbiology: La Presse Medicale offers special issue for 1st International Congress for BCG. This includes G. Guerin's appreciation of A. Calmette (1895–1919) and A. Courcoux's statistics and discussion of modifications (*Presse Med.*, 1/405–413/June 12/48). H. Lara discusses quantum mechanism of epidemicity (*Acta Med. Philippina*, 4/1–56/48). E. W. Lowman and R. J. Boucek report prompt remission in Reiter's disease (spirochaetosis) with hyperthermia and penicillin (*Ann. Int. Med.*, 28/1075/48). E. Diqzfalusy and H. von Euler claim that resistance to streptomycin develops easily, quickly and specifically

(*Ark. Kemi. Min. Geol.*, 25/B4/1/48). Neat is L. Pauling's article on antibodies and specific biological forces (*Endeavour*, 7/43/48). E. Chain well discusses chemical properties and structure of penicillins (*ibid.*, pp. 83). J. E. Smadel and others report chloromycetin (20–40 mgm/Kg/day) is effective in typhus fever with no untoward side actions (*Proc. Soc. Exp. Biol. Med.*, 68/12/48). C. A. Elvehjem discusses nutritional significance of intestinal flora (*Fed. Proc.*, 7/410/48).

4. MISCELLANEOUS: A. C. Ivy pontificates on history and ethics of use of human subjects in medical experiments (*Science*, 108/1/July 2/48). J. C. Trent offers Walt Whitman as a case history in chronic Tb (*Surg. Gyn. Obs.*, 87/113/48). E. Tortonese describes Lazzaro Spallanzani (1661–1730) as founder of experimental physiology (*Endeavour*, 7/92/48). *Letheon* gets a puff (*Med. J. Austral.*, 1/653/May 22/48). P. Forssel studies fluid balance in infantile intoxication (*Ann. Med. Inter. Fenniae*, 37/16/48). M. Nickerson and L. S. Goodman discuss adrenergic blockade with reference to dibenamine (*Fed. Proc.*, 7/397/48). I. Heilbron notes role of chemistry in combating tropical diseases (*Nature*, 161/956/June 19/48). Congratulations to Prof. G. van Rijnberk on the festschrift in his honor containing fine articles by L. Lapicque (neuro-muscular excitability), A. Querido (permeability of blood-brain barrier), H. Veen (air content of lungs in drowning), H. D. Bouman (polio physiology) and others (*Arch. Neerl. Physiol.*, 28/670/47).